FORM PTO-1390 (REV 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		33339/208804 U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) To be assigned 09/762194
INTERNATIONAL APPLICATION NO. PCT/FR99/01908	INTERNATIONAL FILING DATE August 2, 1999	PRIORITY DATE CLAIMED August 4, 1998

TITLE OF INVENTION

NUCLEIC SEQUENCES CODING FOR AN AT2 INTERACTING PROTEIN INTERACTING WITH THE AT2 RECEPTOR AND THEIR APPLICATIONS

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).

4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

[redacted]

JC02 Rec'd PCT/PTO 05 FEB 2001

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) To be assigned 09/762194	INTERNATIONAL APPLICATION NO. PCT/FR99/01908	ATTORNEY'S DOCKET NUMBER 33339/

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00** International preliminary examination fee (37 CRF 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00** International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search (37CFR 1.445(a)(2)) paid to USPTO **$710.00** International preliminary examination fee (37 CFR 1.482) paid to USPTO But all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00** International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$ 100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	20 -20 =	0	**X $18.00**	**$ 0.00**	
Independent Claims	2 - 3 =	0	**X $80.00**	**$ 0.00**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $270.00**	$	

TOTAL OF ABOVE CALCULATIONS =	**$ 860.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by one-half.	$	
SUBTOTAL =	**$ 860.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$	
TOTAL NATIONAL FEE =	**$ 860.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$	
TOTAL FEES ENCLOSED =	**$ 860.00**	
	Amount to be Refunded	$
	Charged	$

a. ☒ A check in the amount of $ 860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 16-0605 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-0605.

Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

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Attorney's Docket No. 33339/208804 PATENT

IN THE UNITED STATES DESIGNATED OFFICE (DO/US)

In re: Attn: DO/US
International Appl. No. PCT/FR99/01908
International Filing Date: August 2, 1999
For: NUCLEIC SEQUENCES CODING FOR AN AT2 INTERACTING PROTEIN INTERACTING WITH THE AT2 RECEPTOR AND THEIR APPLICATIONS

STATEMENT IN SUPPORT OF FILING A SEQUENCE LISTING UNDER 37 CFR § 1.821(f)

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Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted concurrently herewith in accordance with 37 CFR § 1.821(c) and (e), are the same.

Respectfully submitted,

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NUCLEIC SEQUENCES ENCODING AN AT2 RECEPTOR-INTERACTING PROTEIN (ATIP) AND THEIR APPLICATIONS

The present invention relates to nucleic sequences encoding a protein capable of interacting with the AT2 receptor, to oligonucleotides contained in the said sequences, to their applications as probes and for the expression of the said proteins, to the vectors useful for the said expression, to the host cells containing the said vectors and to a model for studying the AT2 receptor.

The present invention also relates to the said proteins and to their applications.

The octapeptide, angiotensin II, mainly known as a regulator of blood pressure, has also been described as an important modulator of cell growth. Interestingly, this peptide appears to exert opposite effects on cell growth according to whether it is bound to one or the other of its two subtypes of membrane receptors (AT1 or AT2).

The AT2 receptor subtype, which also belongs to the G protein-coupled receptor family, is still poorly characterized both from the point of view of its mechanisms of activation and its physiological role (C. Nahmias et al., *Trends Pharmacol Sci*, 1995, 16, 223-225). Several arguments suggest, however, a role for this receptor in the phenomena of cell proliferation, differentiation or adhesion.

The AT2 receptor is highly expressed during foetal life, disappears in adults in most tissues, but becomes reexpressed under pathophysiological conditions involving restructuring of the tissues.

Studies carried out *in vivo* have demonstrated the inhibitory role exerted by the AT2 subtype on the proliferation of the muscle cells of the *tunica intima vasorum* after vascular lesion (P. Janiak et al., *Hypertension*, 1992, 20, 737-745; M Nakajima et al., *Proc. Natl. Acad. Sci.* USA, 1995, 92, 10663-10667).

Moreover, the stimulation of the AT2 receptor activates phosphatase SHP-1 (Bedecs K., et al; *Biochem. J.*, 1997, 325, 449-454). The fact that the AT2 receptor activates a phosphatase is consistent with its antiproliferative effects.

In the light of the above, it has been shown that, on cells in culture, the AT2 receptor:

- inhibits the synthesis of DNA and proliferation, which are induced by angiotensin II (Ang II) and bFGF (M. Stoll et al., *J. Clin. Invest.*, 1995, 95, 651-657),
- induces apoptosis (T. Yamada et al., *Proc. Natl. Acad. Sci. USA*, 1996, 93, 156-160), and
- induces neuronal differentiation (L. Laflamme et al., *J. Biol. Chem.*, 1996, 271, 22729-22735).

Studies of the signalling pathways associated with the AT2 receptor have been undertaken in cells of the N1E-115 line which are derived from a murine neuroblastoma and which express only the AT2 subtype. A first study has made it possible to demonstrate rapid and transient dephosphorylation of some proteins on the tyrosine residues following the treatment of N1E-115 cells with angiotensin II (C. Nahmias et al., *Biochem. J.*, 1995, 306, 87-92). It has also been shown that the AT2 receptor interferes with the pathways for activation of growth factor receptors and inhibits the activity of MAP kinases (ERK1 and ERK2) *(mitogen-activated protein)*, which play a key role in the phenomena of cell proliferation and differentiation. The inhibitory effect of AT2 on the activation of MAP kinases is rapid and transient, does not involve a regulatory protein sensitive to the pertussis toxin (of the Gi/Go type), but involves the activation of an orthovanadate-sensitive tyrosine phosphatase.

Taking into account the role of the AT2 receptor in cell proliferation, the inventors have sought to develop tools capable of regulating the action of the AT2 receptor. Indeed, the activation of

the AT2 receptor may have repercussions in cancerology (inhibition of cell proliferation).

In general, the AT2 receptor has opposite effects to those of AT1 on the activation of MAP kinases and on cell proliferation; study of the communication which may exist between these two receptor subtypes, which bind the same ligand, is consequently of interest.

The study of the signalling pathways and of the regulation of the AT2 receptor also represents a major stake for human health knowing that antagonists of the AT1 receptor are currently administered to patients with hypertension. In this context, it is essential to know the biological effects associated with the AT2 receptor which remains activable by circulating Ang II in this type of treatment.

The subject of the present invention is an isolated nucleic acid (DNA or RNA) fragment, encoding a protein capable of binding to the AT2 receptor, which fragment is selected from the group consisting of the sequences SEQ ID NO:1, 3, 5, 7 and 9, as represented in the sequence listing included in the present application.

These various sequences correspond to the complementary DNA (cDNA) encoding all or part of the protein called hereinafter ATIP (*AT2 interacting protein*).

The sequence SEQ ID NO:1 (1803 bp) corresponds to the complete nucleic sequence of mouse ATIP and includes both the parts encoding the AT2 receptor binding protein and the noncoding parts.

The sequence NO:3 (1323 bp) corresponds to the nucleic acid sequence of the coding part of the sequence SEQ ID NO:1, while the sequence SEQ ID NO:5 corresponds to the sequence NO:1 fragment obtained by the two-hybrid technique (A Plessis et al., M/S, 1994, 9, I-1K; J. Luban et al., *Curr. Op. Biotechnol.*, 1995, 6, 59-64).

The sequence SEQ ID NO:7 (3742 bp) corresponds to the complete nucleic sequence of the human cDNA and includes both the parts encoding the protein homologous to the mouse ATIP and the noncoding parts.

The sequence SEQ ID NO:9 (1308 bp) corresponds to the coding part of the sequence SEQ ID NO:7.

The subject of the present invention is also transcripts, characterized in that they are complementary to the sequences in accordance with the invention and are in particular generated from the said sequences.

The subject of the present invention is, in addition, fragments of the said sequences comprising between 20 and 400 bp, useful as probes or as primers, for the detection of the sequences SEQ ID NO:1, 3, 5, 7 or 9, or of homologous sequences.

Among the said fragments, there may be mentioned in particular a probe of 354 bp (SEQ ID NO:5) as well as any fragment of 20 bp to 400 bp included in the sequences SEQ ID NO:1, 3, 5, 7 or 9.

As primer, there will be used in particular the sequence SEQ ID NO:10 (antisense oligonucleotide) which makes it possible in particular to amplify the 5' parts of the various mRNAs corresponding to ATIP (5' RACE technique: Marathon cDNA amplification kit, Clontech).

It is also possible to use, as amplification primers, any pair of oligonucleotides of more than 20 bp and comprising part of the ATIP (human or mouse) nucleic sequence, in particular the pair SEQ ID NO:11-SEQ ID NO:12.

The preferred hybridization (prehybridization and hybridization) conditions are in particular the following: 45% formamide, 9% dextran sulphate, 0.2% BSA, 0.2% polyvinyl pyrrolidone, 0.2% Ficoll, 0.1% sodium pyrophosphate, 0.01% SDS, 0.05 mM Tris pH 7.5, 0.9 M NaCl and rinses to a stringency corresponding to the buffer: 1XSSC, 0.1% SDS.

The subject of the present invention is also a purified and isolated protein, called ATIP, which is capable of interacting with the AT2 receptor and which is selected from the group consisting of the sequences SEQ ID NO:2, 4, 6 or 8.

The murine and human sequences exhibit 85.6% homologies. The human sequence (human ATIP) possesses 5 amino acids less than the mouse sequence (mouse ATIP). The amino acids missing from the human sequence are situated at the level of amino acids: 162, 163, 164, 166 and 214 of the mouse ATIP sequence.

Comparisons (Blast) between the ATIP protein sequences according to the invention and the sequences contained in data banks indicate that human ATIP (like mouse ATIP) never exhibits more than 25% homology with a known sequence, and this being the case only over part of this sequence.

The subject of the present invention is also a translational product, characterized in that it is encoded by a nucleotide sequence in accordance with the invention.

The subject of the present invention is, in addition, antibodies, characterized in that they are directed against the ATIP protein or an ATIP protein fragment according to the invention.

The subject of the present invention is also a recombinant cloning and/or expression vector, characterized in that it comprises a nucleotide sequence in accordance with the invention.

The subject of the present invention is also a transformed host cell, characterized in that it comprises a vector as defined above.

Among the preferred transformed cells according to the invention, there may be mentioned *E. coli* and CHO cells.

The subject of the present invention is also transformed host cells, characterized in that they consist of a suitable yeast strain cotransformed with

at least two vectors which respectively encode (i) a so-called bait protein selected from the group consisting of a fragment containing at least SEQ ID NO:5 of the ATIP protein and a fragment containing at least the C-terminal end of the AT2 receptor, which bait protein is fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the same transcription factor and (ii) a so-called prey protein, selected from the group consisting of a fragment containing at least SEQ ID NO:5 of the ATIP protein, a fragment containing at least the C-terminal end of the AT2 receptor and any other polypeptide corresponding to a sequence contained in a cDNA library, which prey protein is fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the same transcription factor, which vectors comprise, in addition, selectable markers.

According to an advantageous embodiment of the said cells, they consist in particular of:

- either a suitable yeast strain cotransformed with three vectors which respectively encode (i) a bait corresponding to a fragment containing the C-terminal end of the AT2 receptor fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, (ii) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to the invention, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (iii) a polypeptide corresponding to a sequence contained in a cDNA library, which vectors comprise, in addition, selectable markers,

- or a suitable yeast strain cotransformed with two vectors which respectively encode (i) a fragment

containing at least SEQ ID NO:5 of the ATIP protein according to the invention, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a polypeptide corresponding to a sequence contained in a cDNA library, fused with a protein selected from the group consisting of the DNA-binding domain of the transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers,

- or a suitable yeast strain cotransformed with two vectors, namely (i) a vector encoding a fragment containing at least SEQ ID NO:5 of the ATIP protein, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a vector encoding a fragment containing the C-terminal end of the AT2 receptor, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, one of the two vectors necessarily encoding a mutated protein.

The subject of the present invention is also a method for selecting proteins inhibiting ATIP protein according to the invention-AT2 receptor interaction, which method comprises:

(a) cotransforming a suitable yeast strain with three vectors which respectively encode (i) a bait corresponding to a fragment containing the C-terminal end of the AT2 receptor fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, (ii) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to the invention, fused with a protein selected from the

group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (iii) a polypeptide corresponding to a sequence contained in a cDNA library, which vectors comprise, in addition, selectable markers,

(b) selecting the clones of cDNA library expressing a polypeptide inhibiting the AT2 receptor-ATIP protein according to the invention interaction, on an appropriate selective medium, and

(c) identifying the said polypeptide.

Such a method uses in particular the so-called reverse two-hybrid or three-hybrid technique as described in Vidal et al. (*Proc. Natl. Acad. Sci.* USA, 1996, **93**, 10315-10320 and 10321-10326) or Tirode et al. (*J. Biol. Chem.*, 1997, **272**, 37, 22995-22999).

The subject of the present invention is also a method for screening polypeptides interacting with the ATIP protein according to the invention, which method comprises:

(a) cotransforming a suitable yeast strain with two vectors as defined above, namely which respectively encode (i) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to the invention, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a polypeptide corresponding to a sequence contained in a cDNA library, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, and

(b) selecting the clones expressing a polypeptide interacting with the ATIP protein, on a suitable selective medium.

Such a method makes it possible in particular to search for other proteins interacting with the ATIP

protein, in particular in order to find the next links in the pathway activated by the AT2 receptor, so as to use them to modify the protein according to the invention-AT2 receptor interaction.

The subject of the present invention is also a method for characterizing the domains involved in the ATIP protein-AT2 receptor interaction, characterized in that it comprises:

(a) cotransforming a suitable yeast strain with two vectors, as defined above, namely (i) a vector encoding a fragment containing at least SEQ ID NO:5 of the ATIP protein, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a vector encoding a fragment containing the C-terminal end of the AT2 receptor, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, one of the two vectors necessarily encoding a mutated protein, and

(b) visualizing, by selection on a suitable selective medium, the possible loss of the ATIP-AT2 receptor interaction.

Such a method makes it possible to identify and to delimit the important domains of the ATIP protein or of the C-terminal end of the AT2 receptor, on which their interaction depends, so as to use them as preferred target for modifying the AT2 receptor signalling.

The subject of the present invention is also a method for selecting substances capable of influencing the ATIP protein according to the invention-AT2 receptor interaction, which method comprises:

(a) bringing the ATIP protein, attached to a support, into contact with a fusion protein AT2

receptor-protein tag, optionally in the presence of a substance to be tested,

(b) at least one washing of the said support thus treated with a suitable buffer, and

(c) visualizing the possible ATIP-AT2 receptor interaction, in particular in SDS-PAGE, followed by immunoblotting with antibodies directed against the protein tag, fused with the AT2 receptor, or against the AT2 receptor.

If the substance to be tested inhibits the ATIP-AT2 receptor interaction, the visualization step is negative.

In accordance with the invention, ATIP is attached to the said support either covalently, or through affinity binding between an attachment substance fused with ATIP and the said support. For example, the said support consists of beads coupled either to a substance having affinity with the said attachment protein, fused with ATIP, or to suitable antibodies.

The fusion protein AT2 receptor-protein tag is in particular obtained from a lysate of cells transfected with a vector expressing the fusion protein AT2-protein tag.

As a variant, the said method for selecting substances capable of interacting with the ATIP protein according to the invention comprises:

(a) bringing the ATIP protein, attached to a support, into contact with a cell lysate,

(b) at least one washing of the said support thus treated with a suitable buffer,

(c) visualizing the possible protein combined with the ATIP protein, in particular in SDS-PAGE, followed by immunoblotting with appropriate antibodies, and

(d) identifying the protein in the cell lysate interacting with the ATIP protein.

In accordance with the said method for selecting substances capable of influencing the ATIP protein according to the invention-AT2 receptor interaction, it is possible to use in particular, as fusion proteins ATIP-protein tag, the proteins GST-ATIPc and MYC-ATIPc, which constitute tools which can make it possible to bring down *in vitro* any proteins interacting with ATIP, for example, from cell lysates activated or otherwise with ligands for the AT2 receptor. The GST-ATIP protein may be brought down by specific interaction of GST with agarose beads coupled to glutathione, or alternatively immunoprecipitated with the anti-ATIP antibody. The *Myc*-ATIP protein may be immunoprecipitated with commercial anti-MYC antibodies or with the anti-ATIP antibody.

The advantage of these methods consists in finding means of modifying the signalling, the level of expression or the pharmacology of the AT2 receptor, which may have therapeutic applications. Indeed, when a pathological condition has been clearly correlated with a transduction abnormality associated with the AT2 receptor, modification of this transduction, in particular by acting on the binding of the AT2 receptor to the protein according to the invention, may then possibly compensate for the pathological disorder or at least influence it.

The subject of the present invention is also the use of the abovementioned cotransformed cells for the selection and screening of substances or of proteins capable of influencing the ATIP protein-AT2 receptor interaction or capable of interacting with the ATIP protein.

In addition to the preceding features, the invention also comprises other features which will emerge from the description which follows, which refers to exemplary embodiments of the method which is the subject of the present invention as well as to the accompanying drawings, in which:

- Figure 1 corresponds to the C-terminal end of the mouse AT2 receptor, used as a two-hybrid bait for screening a mouse cDNA library;

- Figure 2 illustrates the position of the GAL4-binding domain and the multiple cloning site of the plasmid pGBT9 (Clontech);

- Figure 3 illustrates the presumed *coiled-coil* structures (*coiled-coil* domains underlined) of mouse ATIP;

- Figure 4 illustrates the presumed *coiled-coil* structures (*coiled-coil* domains underlined) of human ATIP;

- Figure 5 illustrates the structure of the plasmid pVP16;

- Figure 6 illustrates the multiple cloning site of the plasmid pRSET A;

- Figure 7 illustrates the MCY sequence used to construct the plasmid pcDNA3-MYC;

- Figure 8 illustrates the structure of the plasmid pBAC-PAK-poly HIS;

- Figure 9 illustrates a Northern blot of several human tissues hybridized with the probe ATIPmouse-short (SEQ ID NO:5);

- Figure 10 illustrates the interaction *in vitro* of the protein ATIPmouse-short with the C-terminal end of the AT2 receptor; and

- Figure 11 illustrates the modifications of the signal induced by the AT2 receptor by overexpression of the ATIP protein.

It should be clearly understood, however, that these examples are given solely by way of illustration of the subject of the invention and do not constitute in any manner a limitation thereto.

EXAMPLE 1: Demonstration of a specific protein-protein interaction between the AT2 receptor and the protein having the sequence SEQ ID NO:6 according to the invention

Materials and methods

- The two-hybrid system, initially developed by Song and Fields in 1989 (Nature, **340**, 245-246) is based on the fact that the activity of numerous eukaryotic transcription-activating factors requires only two domains: an activating domain which does not have the capacity to bind DNA and a DNA-binding domain.

In the two-hybrid system, the DNA-binding domain is fused with a protein X and the activation domain is fused with a protein Y. If, and only if, X and Y interact, a complex is formed which reconstitutes a functional transcription factor.

- Construction of the expression vectors:

. "bait" vectors:

Protein X: C-terminal end of the sequence encoding the mouse AT2 receptor (52 amino acids of CVNPF at the stop codon, see Figure 1), fused with the sequence encoding the Gal4 DNA-binding domain (Figure 2).

Insert: end of the mouse AT2 receptor (159 bp + 16 bp of sites generated by PCR) inserted at the level of the EcoRI and BamHI sites of the vectors pLEX9 (Clontech) or pGBT9 (modified pGAD424 or pBTM116; A.B Vojtek et al., Cell, 1993, **74**, 205-214).

The following sequence is thus obtained:
CGGAATTC on the 5' side-AT2 C-terminal sequence of 52 amino acids-GGATCCCG 3' side

. screened library:

mouse foetal cDNA library (A.B. Vojtek et al., *Cell*, 1993, **74**, 205-214), containing inserts of 350 to 700 bp (protein Y) in the vector VP16 (Figure 5).

. "Bait" control vectors

Protein X: C-terminal end of the human β2-adrenergic receptors, rat AT1 or human bradykinin.

. Transformed yeast strain

HF7c (Clontech) for the bait constructed in pGBT9;

L40 for the bait constructed in pLex9.

Results

This strategy made it possible to isolate a clone derived from the cDNA library containing an insert of 354 bp (ATIP) which interacts specifically with the C-terminal end of AT2. It is of interest to note that the screening of this library with the constructs produced in the two expression vectors pGBT9 and pLEX9 made it possible to find this same clone in both cases. This clone does not interact with control proteins exhibiting nonspecific interactions.

To evaluate the selectivity of this interaction, the ATIP clone was tested as a two-hybrid system with the C-terminal ends of the receptors: human β2 adrenergic, rat AT1 and human bradykinin, and all gave negative results. This indicates that the polypeptide encoded by the ATIP clone interacts, in a selective manner, with the C-terminal end of the mouse AT2 receptor.

EXAMPLE 2: Characterization of the ATIP clone

To test for the corresponding whole clone, a probe of 354 bp (SEQ ID NO:5), which corresponds to the insert obtained by digestion with the restriction enzyme NotI of the plasmid isolated in a two-hybrid system (that extracted from the VP16 library, selected as being positive in the screen using, as bait, the C-terminal end of the mouse AT2 receptor), is used to screen a mouse foetal cDNA library constructed with inserts of more then 1 kb in size. Two overlapping clones, comprising the ATIP sequence, were thus identified and made it possible to sequence 1803 bp of the corresponding cDNA (SEQ ID NO:1). This sequence contains an open reading frame of 1323 bp (SEQ ID NO:3), potentially encoding a protein of 440 amino acids (SEQ ID NO:2 and 4). Comparisons between the

identified protein sequence and the sequences contained in data banks indicate that it never exhibits more than 25% homology with a known sequence part.

The 354 bp probe (SEQ ID NO:5) was used as probe in Southern and Northern in a very satisfactory manner under the hybridization conditions below: prehybridization and hybridization in 45% formamide, 9% dextran sulphate, 0.2% BSA, 0.2% polyvinylpyrrolidone, 0.2% Ficoll, 0.1% sodium pyrophosphate, 0.01% SDS, 0.05 mM Tris pH 7.5, 0.9 M NaCl and rinses to stringency: 1 x SSC, 0.1% SDS.

In parallel, Northern blot hybridization experiments carried out on total RNAs of N1E-115 cells with the ATIP probe (SEQ ID NO:5) confirm the expression of the corresponding mRNA in the N1E-115 cells, and indicates the existence of at least 5 transcripts of different sizes. These transcripts correspond to alternative splicings of the same gene or to different homologous genes.

On a Northern, performed under the conditions described in the literature on a 5 µg sample of poly A+ RNA of N1E-115 cells, the sizes of the various transcripts hybridizing with the ATIPmouse probe are = 2.5-3.5-5-5.3 and 7.5 kb.

Figure 9 represents a Northern blot containing poly A+ RNAs of various human tissues, hybridized with the same ATIPmouse probe. It is possible to observe that ATIP is ubiquitously expressed. A predominant transcript at 4.4 kb is found in all the tissues represented, to which there are added, according to the tissues, other longer transcripts (pancreas and heart) or shorter transcripts (pancreas, skeletal muscle, placenta, brain and heart). These are perhaps the fruit of an alternative splicing of the ATIP RNA which would be dependent on the tissue considered or alternatively they are the sign of the existence of an RNA family encoding proteins of the "ATIP family" homologous to

ATIP and which are revealed by the probe, at the stringency used.

To know the size of the smallest transcript encoding ATIP, a rapid amplification of the cDNA ends (5' RACE, Marathon cDNA Amplification Kit from Clontech) from poly A+ RNA of N1E-115 cells was carried out using the antisense oligonucleotide of SEQ ID NO:10, to amplify the 5' parts of the various mRNAs corresponding to the endogenous ATIP of the N1E-115 cells (murine neuroblastoma).

The results obtained indicated that the smallest transcript including the ATIP domain is an mRNA of 1950 bp, which indeed contains the start of the coding sequence obtained by cloning.

Any other pair of oligonucleotides (primers) of more than 20 bp and comprising part of the ATIP sequence may also be used to amplify, by PCR (PCR conditions to be determined for each pair of oligonucleotides with the aid of the OLIGO 4 software), part of the ATIP (and to give a DNA fragment which may be optionally used as a probe to recognize the DNA or the RNA corresponding to the ATIP).

EXAMPLE 3 Construction of various vectors according to the invention

In general, the vectors containing ATIPmouse-short (with the exception of pRSETA-ATIPmouse-short) were obtained from an insert produced by PCR with the following two oligonucleotides (SEQ ID NO:11 and SEQ ID NO:12):

oligo. sense: 5' CGCGGATCCCAGACAGACCGGACGGAACTGGAG3'

oligo. antisense: 5'CCGGAATTCACTACAACCTTTCGTTTAAAGCATC 3',

using as template the vector VP16-ATIPmouse-short (Figure 5). For the sake of convenience, this vector is called $^{B}ATIPc^{stop,E}$. Indeed, digested with BamHI and EcoRI, it gives an insert corresponding to the sequence

1st strand: GATCC-SEQ ID NO:5 (minus CAT)-TAGTG
2nd strand: CCTAG----------CTTAAG
(STOP)

BamHI site EcoRI site

Other vectors may also be constructed; they comprise all or part of the ATIP protein and are the following:

-VP16-ATIPmouse-short (vector taken from the library screened in the two-hybrid system, comprises 354 bp (SEQ ID NO:5), inserted in NotI into VP16).

-pCDNA3-MYC-ATIPmouse-short (insert $^{B}ATIPc^{stop,E}$, inserted in BamHI-EcoRI into pCDNA3-MYC (pcDNA3 from Invitrogen, modified by insertion of the MYC sequence, Figure 7); this plasmid may be used in stable or transient transfections. It makes it possible to express MYC-ATIPmouse-short in eukaryotic cells. The expression of this protein in eukaryotic cells after transfection of the corresponding plasmid has already been obtained and checked by immunoreaction with an anti-MYC and anti-ATIP antibody.

-pRSETA-HIS-ATIPmouse-short (insert $^{B}ATIPc^{stop,E}$, inserted in BamHI-EcoRI into pRSETA, Invitrogen). This plasmid makes it possible to express the fusion protein HIS-ATIPmouse-short in bacterial cells and to purify it on a nickel column (see Figure 6 for the multiple cloning site).

-pBacPAK-polyHIS-ATIPmouse-short (insert $^{B}ATIPc^{stop,E}$, inserted in BamHI-EcoRI into the vector pBacPAK-polyHIS (commercial pBacPAK, modified by insertion of a sequence containing a histidine tag and a site for cleavage with thrombin, Figure 8). This construct may be used to express the ATIPmouse-short protein, fused with a histidine tag, in insect cells (SF9 type). Indeed, as indicated, this vector contains a poly-histidine insert and can therefore encode the fusion protein. The latter, like the fusion protein cloned into pRSET, may be purified on a nickel column and may serve in the same type of techniques.

-pGEX-4T1-GST-ATIPmouse-short (insert amplified by the PCR identical to $^{B}ATIPc^{stop,E}$, but with no STOP codon, which extends the ATIPmouse-short sequence by the few amino acids which follow: Phe-Glu-Phe-Pro-Gly-Arg-Leu-Glu-Arg-Pro-His-Arg-Asp obtained from the plasmid pGEX-4T-1 (Pharmacia). This plasmid makes it possible to express the protein GST-ATIPmouse-short in bacterial cells and to purify it on glutathione-agarose beads.

-pCDNAI-ATIPmouse clone1 (entire 5' sequenced from ATIP and ORF up to bp: 1205 starting from the beginning of the clone, inserted in BstxI into pCDNAI). This plasmid is derived from the cloning of the mouse foetal library with the probe SEQ ID NO:5. This plasmid can serve to produce, in bacteria, the 5' portion of the ATIPmouse DNA, so as to use it as a probe.

-pCDNAI-ATIPmouse clone2 (2nd half of the ORF of ATIP from bp: 616 and up to the end of the 3'sequenced (bp 1803), inserted in BstxI into pcDNAI, Invitrogen). This plasmid can serve to produce, in bacteria, the 3' portion of the ATIPmouse DNA, so as to use it as a probe.

-pCDNAI-ATIPmouse-long (clones 1 and 2 placed end to end, using the intermediate SapI site. This plasmid contains the entire ATIPmouse clone, inserted in BstxI into pCDNAI). This plasmid may be used in transient transfections in eukaryotic cells.

-pCDNA3-ATIPmouse-long (whole ATIPmouse from BamHI-XbaI of pCDNAI-ATIPmouse-long, and inserted into pcDNA3, Invitrogen, at these same sites). This plasmid may be used in stable or transient transfections in eukaryotic cells. It made it possible to translate *in vitro* (kit TNT T7 *coupled reticulocytes lysate systems,* Promega) the whole ATIP protein and to observe that its translational product has an apparent molecular weight on gel of 58 kDa. Added to this predominant product are two minor products of 30 and 15 kDa. According to the ATIP sequence, these could correspond to partial

products of translation *in vitro* starting with ATGs other than that at position 178 of SEQ ID NO:1.

EXAMPLE 4: Production of stable clones expressing the ATIPmouse-short or long protein

Stable clones expressing both the human AT2 receptor and ATIPmouse-short (SEQ ID NO:6) or ATIPmouse-long (SEQ ID NO:3) were obtained by transfection.

CHO cells, deficient in dihydrofolate reductase, are transfected with a plasmid containing the region encoding the human AT2 receptor (Bedecs et al., *Biochem. J.* 1997, **325**, 449-454).

The clone selected, CHO-hAT2, expressing 100 fmol of AT2 receptor/mg of protein, is cultured on an HAMF12 medium supplemented with 10% foetal calf serum and used between passages 10 and 30.

This clone was itself transfected with the plasmids pCDNA3-MYC-ATIPmouse-short or pCDNA3-ATIPmouse-long described in Example 3. The selection of the clones stably expressing the ATIP protein (short form or long form) was carried out in a selective medium containing 800 µg/ml of G418. The cell lysates, corresponding to the various selected clones, were subjected to SDS-PAGE followed by immunoblotting and this was incubated with the anti-ATIP polyclonal antibody. The results obtained indicate that various clones expressing various levels of ATIPmouse-short were able to be obtained.

EXAMPLE 5: Production of polyclonal antibodies directed against the SEQ ID NO:6 sequence

To progress in the characterization of this clone, the production of polyclonal antibodies directed against the ATIP domain was undertaken.

For that, a vector encoding a protein corresponding to this domain fused with six histidine residues was constructed.

The following sequence:

GGA TCC-SEQ NO:5-TAG-TGA-ATT

is inserted into the plasmid pRSETA, as defined above.

In this insert, SEQ ID NO:5 does not comprise the first CAT.

The plasmid obtained is expressed in the *E. coli* strain BL 21 (DE3) (F^- ompT$^-$ r_B^- m_B^-) containing the bacteriophage DE3 which carries a DNA fragment containing the *lacI* gene, the *lacUV5* promoter, the start of the *lacZ* gene and the gene encoding T7 RNA polymerase. This fragment is introduced into the *int* gene.

In the presence of DE3, only the lacUV5 promoter, inducible by IPTG directs the transcription of T7 RNA polymerase.

The addition of 0.4 mM IPTG to a culture of BL21 (DE3) cells induces the production of T7 RNA polymerase which, in turn, causes the transcription of the target DNA of the plasmid pRSETA (which allows the translation of the protein binding to the AT2 receptor).

The protein obtained (17 kDa) is purified on a nickel column (Ni-NTA, QuiAexpressionist 07/97, Quiagen), by virtue of the affinity of its six histidine residues for nickel. The protein obtained is then injected into rabbits so as to obtain polyclonal antibodies directed against the ATIP protein. The bleedings obtained have a very good titre.

These antibodies, purified on a GST-ATIP column, after passing through a GST column alone (so as to remove possible GST-specific antibodies and to retain on the GST-ATIP column only the antibodies specific for ATIPmouse-short) may be used successfully to immunoprecipitate and reveal in immunoblotting MYC-ATIPmouse-short from transiently transfected COS cells. Furthermore, this purified antibody also reveals in immunoblotting the ATIPmouse-long protein contained in lysates of COS cells transiently transfected with the plasmid pCDNA3-ATIPmouse-long.

The transfected ATIPmouse-long protein is visualized after SDS-PAGE and immunoblotting with an anti-ATIP antibody, in the form of two polypeptides having apparent molecular weights of 50 and 45 kDa.

This purified antibody was used in immunofluorescence on CHO-hAT2 cells, fixed by a 15-minute treatment with paraformaldehyde (3%). After fixing, the cells are successively treated with solutions of PBS/glycine 50 mM for 20 minutes, PBS/Triton X100 0.1% for 5 minutes and PBS/BSA 0.2% for 15 minutes. They are then successively incubated in solutions containing 15 µg/ml of antibody containing the purified anti-ATIP antibody, and then the anti-rabbit immunoglobulin antibody coupled to rhodamine for 30 minutes. Between each new incubation, three rinses in PBS are carried out. Observations under a fluorescence microscope indicate an expression of the endogenous ATIP protein in the nucleus (predominantly) and in the cytoplasm of the CHO-hAT2 cells.

Some cells show a homogeneous distribution of the fluorescence due to the anti-ATIP antibody in these compartments, whereas other cells which appear more spread out, show a heterogeneous distribution of the fluorescence along the filaments which appear to start from the nucleus and spread up to the plasma membrane of the cell, in an organized network. Additional colocalization experiments should be carried out to determine if these filaments coincide or otherwise with known structures of the cytoskeleton.

EXAMPLE 6: Confirmation of the *in vitro* interaction of the ATIPmouse-short protein with the C-terminal end of the AT2 receptor

To demonstrate the interaction of the ATIPmouse-short protein with the C-terminal end of the AT2 receptor in a system other than that of the two-hybrid system, a protocol which makes it possible to demonstrate this interaction *in vitro* was set up. For that, the fusion protein GST-ATIP as described above

was produced; it is combined through its GST part with glutathione coupled to agarose beads (GA). In parallel, bacteria (DH5α) are transfected with a plasmid (pMAL-c2-AT2, derived from pMAL-c2 from New England Biolabs) encoding a fusion protein between the C-terminal end of the human AT2 receptor (Asn314-Ser363) and MBP (Maltose Binding Protein). These bacteria were cultured and the fusion protein was induced in 0.3 mM IPTG according to the protocol "*pMAL Protein Fusion and Purification System*" from New England Biolabs. After centrifugation of the culture at 4 000 g and solubilization of the pellet obtained in "*column buffer*" (20 mM Tris-HCl, 200 mM NaCl, 1 mM EDTA), another centrifugation at 9 000 g made it possible to recover a supernatant containing a high concentration of MBP-AT2. This supernatant was brought into contact, for 3 hours at 4°C, with glutathione agarose beads coupled to GST protein alone after addition of NaCl so as to have 300 mM final NaCl. This preincubation step makes it possible to remove the nonspecific interactions which may exist between ATIP and GA-GST. The supernatant recovered was brought into contact with the GA-GST-ATIPmouse-short or GA-GSTalone beads overnight at 4°C. After contact, the beads were rinsed three times in 20 mM Tris-HCl buffer, 300 mM NaCl, 1mM EDTA and once in "column buffer". After analysing the beads rinsed in SDS-PAGE and immunoblotting with an anti-MBP antibody (New England Biolabs), a specific retention of the MBP-AT2 protein is observed on GA-GST-ATIPmouse-short beads which is not observed on the GA-GSTalone beads (Figure 10).

This same protocol was carried out with a plasmid expressing MBP-AT1 (C-terminal end of human AT1 receptor (Leu 297-Glu 359)); it indicates that the MBP-AT1 protein is not retained in a specific manner on the GA-GST-ATIPmouse-short beads (Figure 10).

These results confirm those obtained in the two-hybrid system indicating a specific and selective interaction between the protein according to the

invention and the C-terminal end of the AT2 receptor (and not AT1).

EXAMPLE 7: Modification of the transduction of the signal for the AT2 receptor in clones overexpressing the ATIPmouse-long protein

To verify that the ATIP protein interacts *in vivo* with the AT2 receptor, it was evaluated whether an overexpression of this protein modifies a signal induced by the AT2 receptor.

For that, a stable clone of CHO-hAT2 cells expressing the ATIPmouse-long protein (CHO-hAT2-ATIP), obtained according to the methodology described in Example 4, was used; the functional test for the activity of the AT2 receptor developed on the CHO-hAT2 clone which consists in inhibiting the phosphorylation of the IRβ subunit of the insulin receptor induced by its ligand, was reproduced.

Demonstration of an inhibition by the AT2 receptor of the phosphorylation of IRβ induced by insulin in CHO-hAT2 cells:

The CHO-hAT2 cells are inoculated at a density of 3×10^6 cells per dish having a diameter of 15 cm^2. They are made quiescent by 16 hours of deprivation before being treated. The treatment consists in bringing into contact for 5 minutes with 15 ml of F12 medium containing insulin supplemented or otherwise with CGP42112 (selective agonist of the AT2 receptor). After treatment, the cells are solubilized in lysis buffer containing: 50 mM Hepes, pH 7.6, 1% Triton X-100, 20 mM EDTA, 30 mM sodium pyrophosphate, 30 mM sodium fluoride, 2 mM benzamidine, 1 mM sodium orthovanadate, 1 mM phenylmethylsulphonyl fluoride and 1 µg/ml of aprotinin, pepstatin, antipain and leupeptin. The lysates are then subjected to purification on a wheatgerm lectin column, according to the protocol described in Issad, T. et al., (*Eur. J. Biochem.* 1995, **234**, 108-115). After bringing into contact and washings, the lectin beads coupled to

Sepharose (Pharmacia) are recovered in sample buffer containing SDS and the eluted proteins are analysed in SDS-PAGE followed by immunoblotting with anti-phosphotyrosine antibodies (Upstate Biotechnology, Inc.) or anti-IRβ antibodies (described in Issad, T. et al., cited above).

The β subunit of the insulin receptor appears as a polypeptide of 97 kDa whose phosphorylation (visualized by revealing with an anti-phosphotyrosine antibody) increases in a dose-dependent manner with the concentration of insulin. Angiotensin II (100 nM) as well as CGP42112 (100 nM) inhibit this phosphorylation at all the insulin doses tested between 0.1 and 0.001 µg/ml (Figure 11). By way of example, CGP42112 inhibits the phosphorylation of IRβ induced by 0.01 µg/ml by a factor of 64 ± 4% (n=7). This result demonstrates that the AT2 receptor interferes negatively with the signalling pathways for the insulin receptor at the initial stage of its activation, which is its autophosphorylation. These results also provide the first evidence of an interconnection between the signalling pathways for the tyrosine kinase receptors and the receptor with seven transmembrane domains which is AT2.

Reproduction of this methodology on CHO-hAT2-ATIP cells:

When this protocol is carried out on CHO-hAT2-ATIP cells, the inhibition by CGP42112 (100 nM) of the phosphorylation of the insulin receptor obtained for various doses of insulin (0.05, 0.01, 0.005, 0.001 µg/ml) is not observed (Figure 11). This result was reproduced 3 times for each of the insulin doses taking, as positive control in each experiment, the inhibition obtained for the clone CHO-hAT2.

This therefore demonstrates that the overexpression of the ATIP protein in the CHO-hAT2 cells interferes with the AT2 receptor signalling,

which confirms the interaction *in vivo* of the ATIP protein with the AT2 receptor.

Another glycosylated protein, retained on a lectin column, having an apparent weight of 120 kDa, identified as being the newly cloned protein SIRP (Kharitonenkov, A. et al., Nature, 1997, 386, 181-186) is phosphorylated on tyrosine in response to insulin. The phosphorylation of this protein, as well as that of IRβ is inhibited in the presence of CGP42112 in the case of the clone CHO-hAT2 and is not in the case of the clone CHO-hAT2-ATIP. This confirms that the ATIP protein interferes with the signalling pathways for the AT2 receptor. These results indeed show the possible value of the use of the ATIP protein for modifying signalling mediated by the AT2 receptor and for possibly compensating for pathological conditions associated with abnormalities in the regulation of this receptor.

As is evident from the above, the invention is not at all limited to those of its embodiments, implementations and applications which have just been described more explicitly; it encompasses, on the contrary, all the variants thereof which may occur to the specialist in the field, without departing from the framework or the scope of the present invention.

CLAIMS

1. Isolated nucleic acid fragment, encoding a protein capable of binding to the AT2 receptor, which fragment is selected from the group consisting of the sequences SEQ ID NO:1, 3, 5, 7 and 9.

2. Fragment of one of the sequences according to Claim 1, comprising between 20 and 400 bp, useful as probes or as primers, for the detection of the sequences SEQ ID NO:1, 3, 5, 7 or 9, or of homologous sequences.

3. Fragment according to Claim 2, characterized in that it comprises from 20 bp to 400 bp included in the sequences SEQ ID NO:1, 3, 5, 7 or 9.

4. Fragment according to Claim 2 or Claim 3, characterized in that it is selected from the group consisting of the sequences SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12.

5. Transcripts, characterized in that they are complementary to the sequences according to Claim 1.

6. Purified and isolated protein, which is capable of interacting with the AT2 receptor and which is selected from the group consisting of the sequences SEQ ID NO:2, 4, 6 or 8, which protein is called ATIP.

7. Translational product, characterized in that it is encoded by a nucleotide sequence according to Claim 1.

8. Antibodies, characterized in that they are directed against a protein or a protein fragment according to Claim 6 or Claim 7.

9. Recombinant cloning and/or expression vector, characterized in that it comprises a nucleotide sequence according to Claim 1.

10. Transformed host cell, characterized in that it comprises a vector according to Claim 9.

11. Transformed host cells, characterized in that they consist of a suitable yeast strain cotransformed with at least two vectors which respectively encode (i)

a so-called bait protein selected from the group consisting of a fragment containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, and a fragment containing at least the C-terminal end of the AT2 receptor, which bait protein is fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the same transcription factor and (ii) a so-called prey protein, selected from the group consisting of a fragment containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, a fragment containing at least the C-terminal end of the AT2 receptor and any other polypeptide corresponding to a sequence contained in a cDNA library, which prey protein is fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the same transcription factor, which vectors comprise, in addition, selectable markers.

12. Transformed host cell according to Claim 11, characterized in that it consists of a suitable yeast strain cotransformed with three vectors which respectively encode (i) a bait corresponding to a fragment containing the C-terminal end of the AT2 receptor fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, (ii) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (iii) a polypeptide corresponding to a sequence contained in a cDNA library, which vectors comprise, in addition, selectable markers.

13. Transformed host cell according to Claim 11, characterized in that it consists of a suitable yeast

strain cotransformed with two vectors which respectively encode (i) a fragment containing at least the sequence SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a polypeptide corresponding to a sequence contained in a cDNA library, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers.

14. Transformed host cell according to Claim 11, characterized in that it consists of a suitable yeast strain cotransformed with two vectors, namely (i) a vector encoding a fragment containing at least the SEQ ID NO:5 of the ATIP protein sequence according to Claim 6, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a vector encoding a fragment containing the C-terminal end of the AT2 receptor, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, one of the two vectors necessarily encoding a mutated protein.

15. Method for selecting proteins inhibiting ATIP protein according to Claim 6 or Claim 7-AT2 receptor interaction, which method comprises:

(a) cotransforming a suitable yeast strain with three vectors which respectively encode (i) a bait corresponding to a fragment containing the C-terminal end of the AT2 receptor fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the

said transcription factor, (ii) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (iii) a polypeptide corresponding to a sequence contained in a cDNA library, which vectors comprise, in addition, selectable markers,

(b) selecting the clones of cDNA library expressing a polypeptide inhibiting the AT2 receptor-ATIP protein according to Claim 6 or Claim 7 interaction, on an appropriate selective medium, and

(c) identifying the said polypeptide.

16. Method for screening polypeptides interacting with the ATIP protein according to Claim 6 or Claim 7, which method comprises:

(a) cotransforming a suitable yeast strain with two vectors as defined above, namely which respectively encode (i) a fragment containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6 or Claim 7, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a polypeptide corresponding to a sequence contained in a cDNA library, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, and

(b) selecting the clones expressing a polypeptide interacting with the ATIP protein according to Claim 6 or Claim 7, on a suitable selective medium.

17. Method for characterizing the domains involved in the ATIP protein-AT2 receptor interaction, characterized in that it comprises:

(a) cotransforming a suitable yeast strain with two vectors, namely (i) a vector encoding a fragment

containing at least SEQ ID NO:5 of the ATIP protein according to Claim 6, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor and (ii) a vector encoding a fragment containing the C-terminal end of the AT2 receptor, mutated or not, fused with a protein selected from the group consisting of the DNA-binding domain of a transcription factor and the activation domain of the said transcription factor, which vectors comprise, in addition, selectable markers, one of the two vectors necessarily encoding a mutated protein, and

(b) visualizing, by selection on a suitable selective medium, the possible loss of the ATIP protein according to Claim 6 or Claim 7-AT2 receptor interaction.

18. Method for selecting substances capable of influencing the ATIP protein according to Claim 6 or Claim 7-AT2 receptor interaction, which method comprises:

(a) bringing the ATIP protein according to Claim 6 or Claim 7, attached to a support, into contact with a fusion protein AT2 receptor-protein tag, optionally in the presence of a substance to be tested,

(b) at least one washing of the said support thus treated with a suitable buffer, and

(c) visualizing the possible ATIP protein according to Claim 6 or Claim 7-AT2 receptor interaction, in particular in SDS-PAGE, followed by immunoblotting with antibodies directed against the protein tag, fused with the AT2 receptor.

19. Method for selecting substances capable of interacting with the ATIP protein according to Claim 6 or Claim 7, characterized in that it comprises:

(a) bringing the ATIP protein according to Claim 6 or Claim 7, attached to a support, into contact with a cell lysate,

(b) at least one washing of the said support thus treated with a suitable buffer,

(c) visualizing the possible protein combined with the ATIP protein, in particular in SDS-PAGE, followed by immunoblotting with appropriate antibodies, and

(d) identifying the protein in the cell lysate interacting with the ATIP protein.

20. Use of the cotransformed cells according to any one of Claims 10 to 13, for the selection and screening of substances or of proteins capable of influencing the ATIP protein-AT2 receptor interaction or capable of interacting with the ATIP protein.

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(54) **Title:** NUCLEIC SEQUENCES CODING FOR AN AT2 INTERACTING PROTEIN INTERACTING WITH THE AT2 RECEPTOR AND THEIR APPLICATIONS

(54) **Titre:** SEQUENCES NUCLEIQUES CODANT POUR UNE PROTEINE (ATIP) INTERAGISSANT AVEC LE RECEPTEUR AT2 ET LEURS APPLICATIONS

(57) **Abstract**

The invention concerns nucleic sequences coding for a protein capable of interacting with the AT2 receptor, oligonucleotides included in said sequences, their applications as probes and for expressing said proteins, vectors useful for said expression, host cells containing said vectors, and study model of AT2 receptor. The invention also concerns said proteins and their uses. Said isolated nucleic acid fragment coding for a protein capable of binding with the AT2 receptor is selected among the group consisting of the sequences SEQ ID NO: 1, 3, 5, 7 and 9.

(57) **Abrégé**

Séquences nucléiques codant pour une protéine apte à interagir avec le récepteur AT2, oligonucléotides compris dans lesdites séquences, leurs applications en tant que sondes et pour l'expression desdites protéines, vecteurs utiles pour ladite expression, hôtes cellulaires contenant lesdits vecteurs, ainsi qu'un modèle d'étude du récepteur AT2. Protéines ainsi que leurs applications. Ledit fragment d'acides nucléiques isolé, codant pour une protéine apte à se lier au récepteur AT2, est sélectionné dans le groupe constitué par les séquences SEQ ID NO:1, 3, 5, 7 et 9.

C-TERMINAL END AT2 RECEPTOR

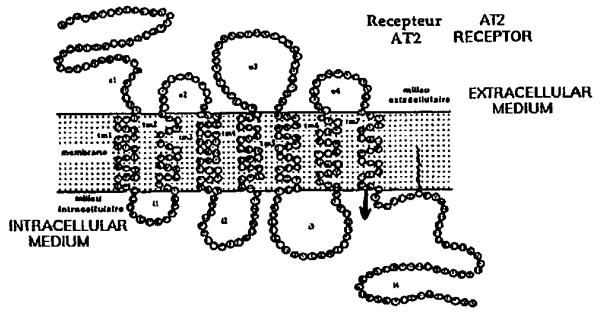
```
LOCUS        Extrémité C-terminale récepteur AT2  160 BP DS-DNA

ORGANISM  Souris MOUSE
BASES        41 A      33 C      36 G      50 T

ac.nucléiques  1 TGTGTTAATC CCTTCCTGTA TTGTTTTGTT GGAAACCGCT
 NUCLEIC ACIDS    TCCAACAGAA CGTCCGCAGT GTGTTTAGAG TTCCCATTAC
                   TTGGCTCCAA GGCAAGAGAG AGACTATGTC TTGCAGAAAA
               121 GGCAGTTCTC TTAGAGAAAT GGACACCTTT GTGTCTTAAA

TRANSLATION INTO AMINOACIDS
Traduction en acides aminés

        CVNPFLYCFV GNRFQQNVRS VFRVPITWLQ GKRETMSCRK
        GSSLREMDTFVS*
```



LOCUS AT2 receptor C-terminal end 160 BP DS-DNA

ORGANISM Mouse
BASES 41 A 33 C 36 G 50 T

Nucleic acids 1 TGTGTTAATC CCTTCCTGTA TTGTTTTGTT GGAAACCGCT
TCCAACAGAA CGTCCGCAGT GTGTTTAGAG TTCCCATTAC
TTGGCTCCAA GGCAAGAGAG AGACTATGTC TTGCAGAAAA
121 GGCAGTTCTC TTAGACAAAT GGACACCTTT GTGTCTTAAA

Translation into amino acids

CVNPFLYCFV GNRFQQNVRS VFRVPITWLQ GKRETMSCRK
GSSLREMDTF VS·

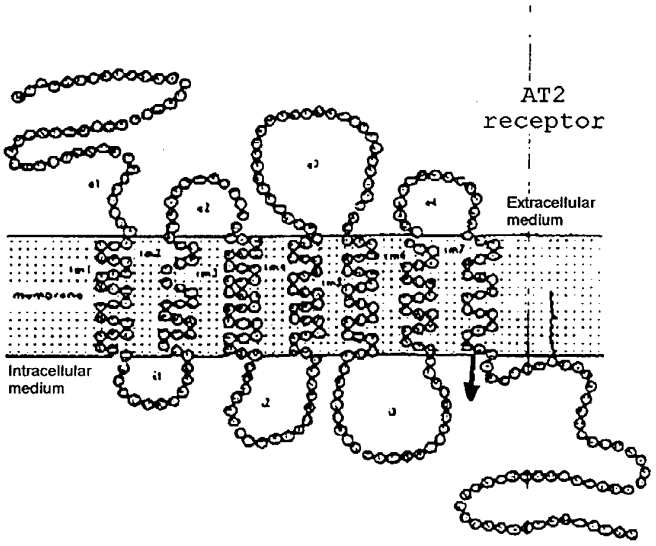


Figure 1

.... AGT AAC AAA GGT CAA AGA CAG TTG ACT GTA TCG
Codon 147
GAL4 DNA-binding domain
Multiple cloning site
SmaI
SalI
CCG GAA TTC CCG GGG ATC CGT CGA CCT...
EcoRI
BamHI

Figure 2

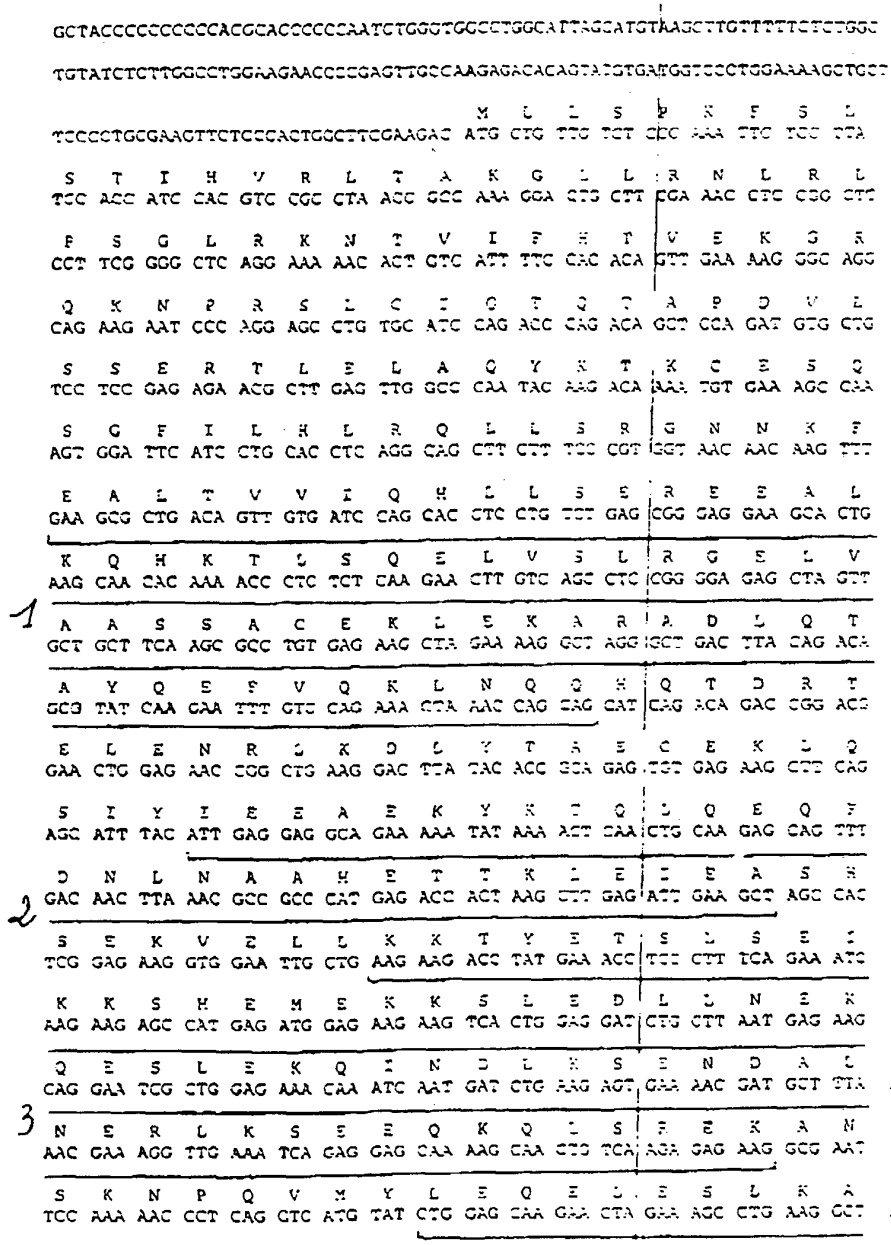


Figure 3.1

4

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 V  L  E  I  K  N  S  K  L  H  Q  Q  D  M  K  L  M  K    333
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 M  E  K  L  V  D  N  N  T  A  L  V  D  K  L  K  R  F    351
ATG GAA AAG CTG GTG GAC AAT AAC ACA GCA TTG GTT GAC AAG CTG AAG CGA TTC   1230

 Q  Q  E  N  E  S  L  K  A  R  M  D  K  H  M  A  I  S    369
CAG CAG GAA AAC GAG GAG TTA AAA GCT CGC ATG GAC AAA CAC ATG GCA ATT TCA   1284

 R  Q  L  S  T  E  Q  A  A  L  Q  E  S  L  E  K  E  S    387
AGG CAA CTT TCC ACC GAG CAG GCC GCG CTG CAA GAG TCC CTT GAG AAG GAG TCA   1338

 K  V  N  K  R  L  S  M  E  N  E  E  L  L  W  K  L  H    405
AAG GTC AAC AAG AGA CTG TCC ATG GAG AAC GAG GAA CTT CTG TGG AAA CTG CAC   1392

 N  G  D  L  C  S  P  K  R  S  P  T  S  S  A  I  P  F    423
AAC GGA GAC CTG TGC AGC CCC AAG AGA TCC CCC ACC TCC TCG GCC ATC CCT TTC   1446

 Q  S  P  R  N  S  G  S  F  S  S  P  S  I  S  P  R  *    440
CAG TCC CCC AGG AAT TCT GGT TCC TTC TCC AGC CCC AGC ATC TCA CCC AGA TGA   1500

CGGCTTCTGAACGCAGGAGACTCTCTGAAGGCACTGAGGTGCGCTTCTGCAGGACTGACCCTCTCATGGGA   1571

ACTCGAGTTGCTGCGTTAGCTCTCTGGAATATCCCCAGGATATCGGGAGAGCAGCCGCCAACCGTATCAGC   1642

TACGTACGAATAGAGAGCTCCAATAGAAGACTTTTAACTTGGTCCAAAAGCCTCCTGCAAAAACAGATTTC   1713

GGAACTGAAGTGGACATAGTTGCACAAAGCACTTACGGAACGAGGGAACCTTGTTCTTTGCCTTCCTTCAC   1784

CTAAGCATAGGCTTTCCAG                                                       1803
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Figure 3c

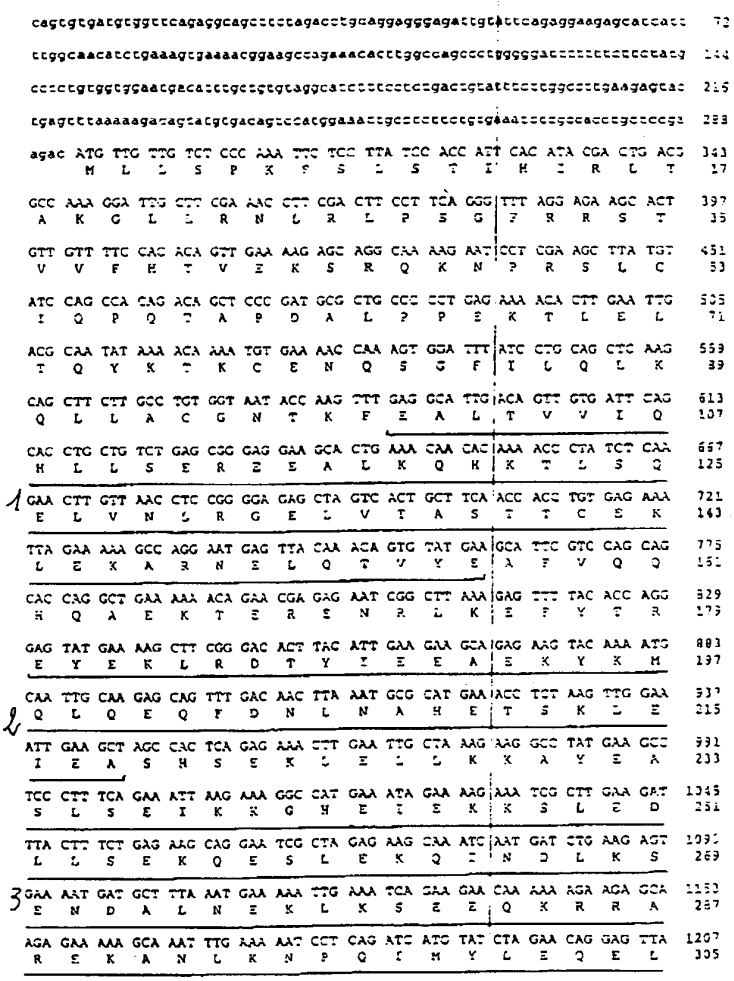

Figure 4

09/762194

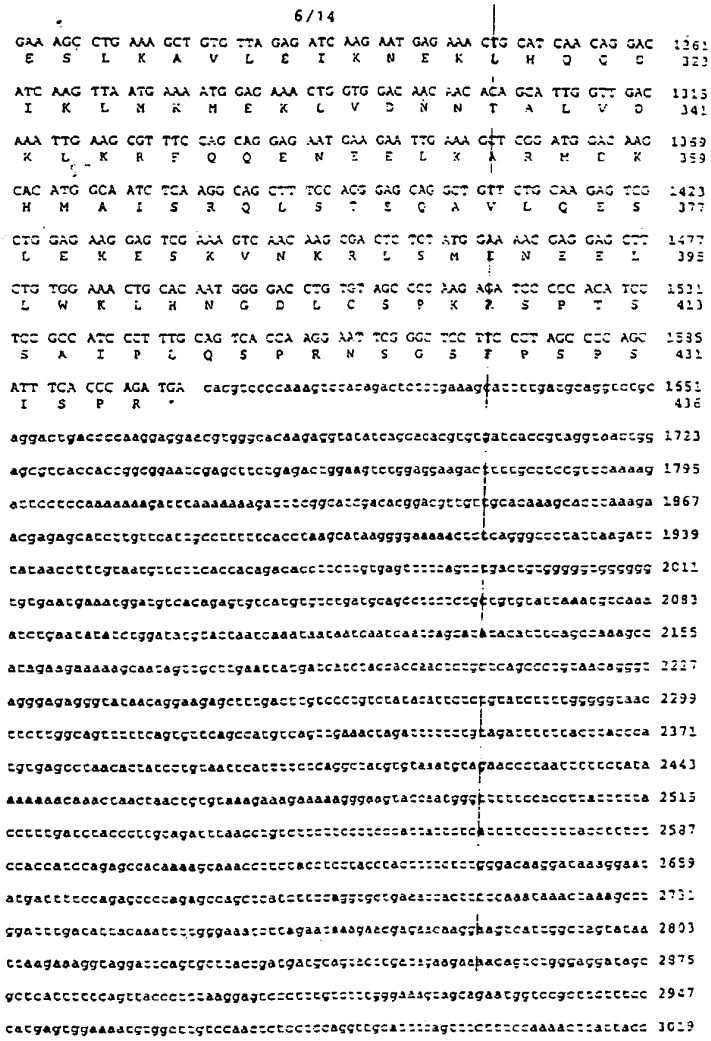

Figure 4.2

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ttcaggatgctcgaggtgaatatttgggtcatttacatgtacactacatagcaagttgatacttcatgttgca 3215
tgttcttttaaaattagtgatttttgtgtcttaagtctttcaacttccaatatttcatcatgtatgtaccctttc 3307
atgtttgcttcctgataaaatggaaacgtaggttcactgccacttcatgagatacctctgcttcacgctttcaag 3379
ttgttcttcaatgacattagccaaagttgggtttgccattcatccccaggcatggtaaatcttgtgttgttc 3451
cctgctgtccttccgtattacgtgaccggcaaataaatcttcatagcagttaaatcaaaacatttttggaggat 3523
gggagagaacaggaggggaagatgggaaacaaaatagagaattccttaagatcttgtttaaaccaaaatgtttca 3595
tgtagaatgcaaaatgttggcacgttcaaaaatatgaatgttgtagacaactgtagttgtgcttcagtttgtagt 3667
gatgggaagtgtattttaccctgatcaaatcaaatcaatgctggaatacttcaaaaaaaaaaaaaaaaaaaaaa 3739
aaa                                                                      3742
```

Figure 4.3

09/762194

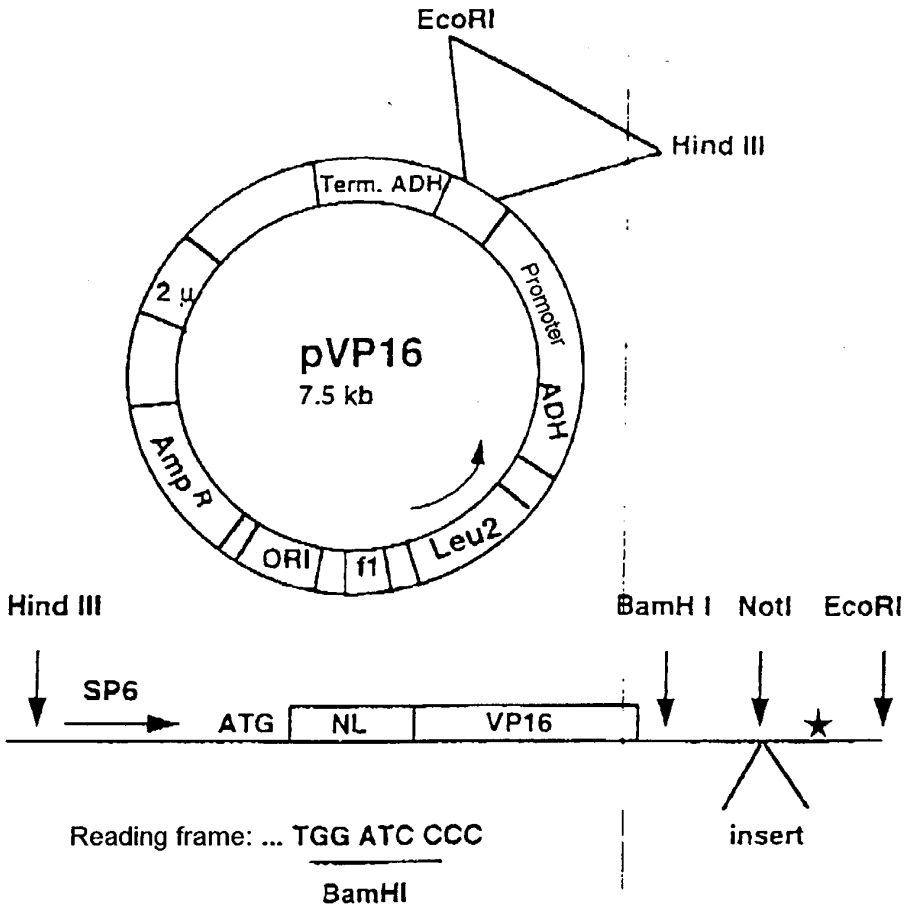


Figure 5

6 histidines

```
98.  ATG CGG GGT TCT CAT CAT CAT CAT CAT CAT GGT ATG

134  GCT AGC ATG ACT GGT GGA CAG CAA ATG GGT CGG GAT

170  CTG TAC GAC GAT GAC GAT AAG GAT CGA TGG GGA TCC
                                        BamH I

206  GAG CTC GAG ATC TGC AGC TGG TAC CAT GGA ATT CGA

242  AGC TTG ATC CGG CTG CTA ACA AAG CCC GAA AGG AAG

278  CTG AGT TGG CTG CCA CCG CTG AGC AAT AAC TAG...
```

Figure 6

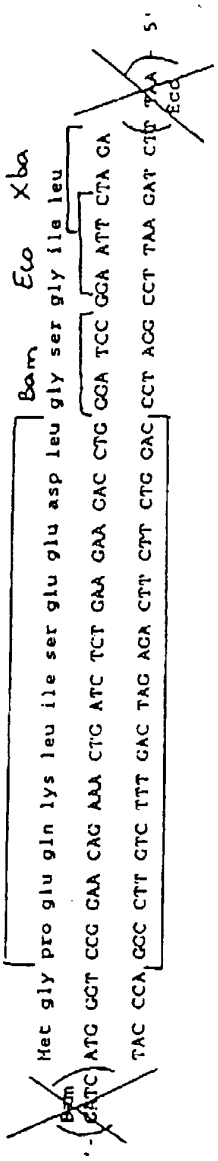
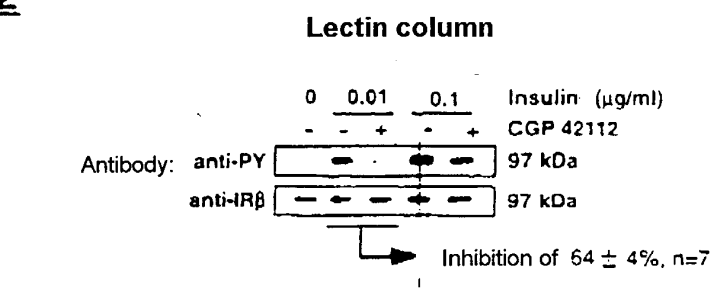
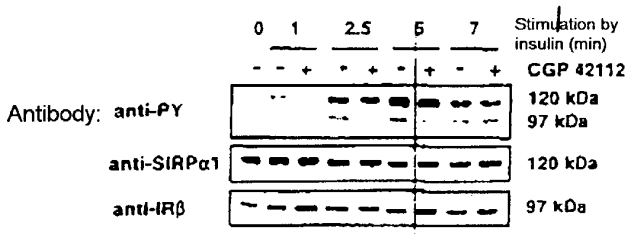

Tag Myc
Bam
Eco
Xba
Met gly pro glu gln lys leu ile ser glu glu asp leu gly ser gly ile leu
5' - GATC ATG GCT CCG GAA CAG AAA CTG ATC TCT GAA GAA GAC CTG CGA TCC CGA ATT CTA GA
TAC CCA GGC CTT GTC TTT GAC TAG AGA CTT CTT CTG GAC CCT AGG CCT TAA GAT CTT TAA 5'
Bam
Eco

Figure 7

09/762194

CHO-hAT2





CHO-hAT2 et CHO-hAT2-ATIP

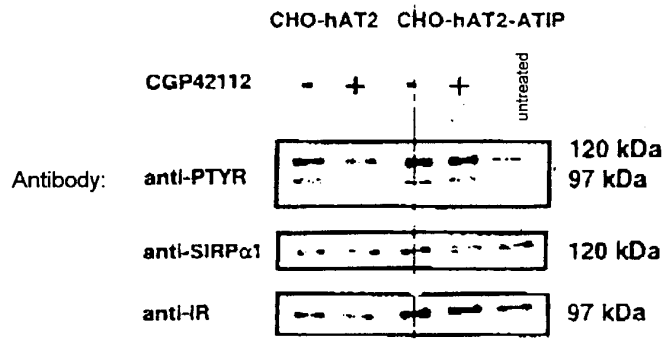
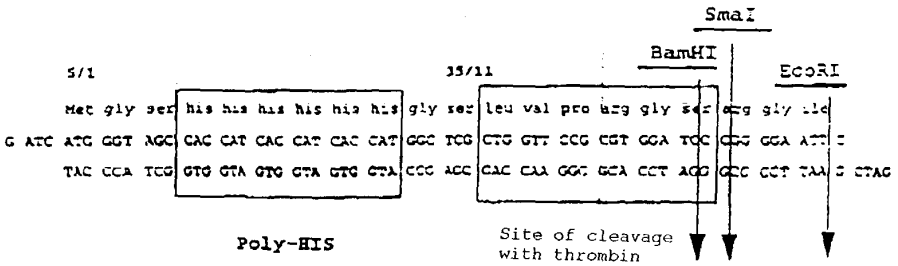


Figure 11



pBacPAK1-poly HIS -> Graphic Map

DNA sequence 5526 b.p. AACGGCTCCGCC . . TCATTAATGCAC circular

PolyHIS insertion into pBackpack in BamHI(CACCAT) 1270-1287

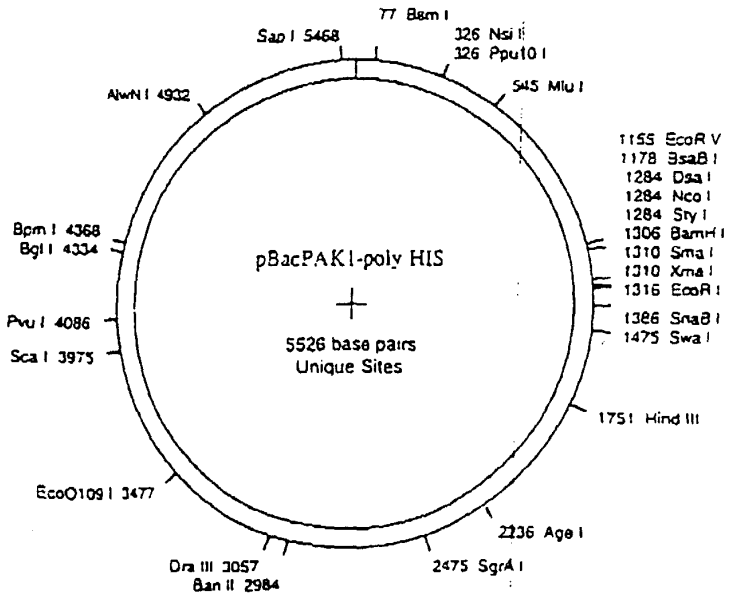


Figure 8

09/762194

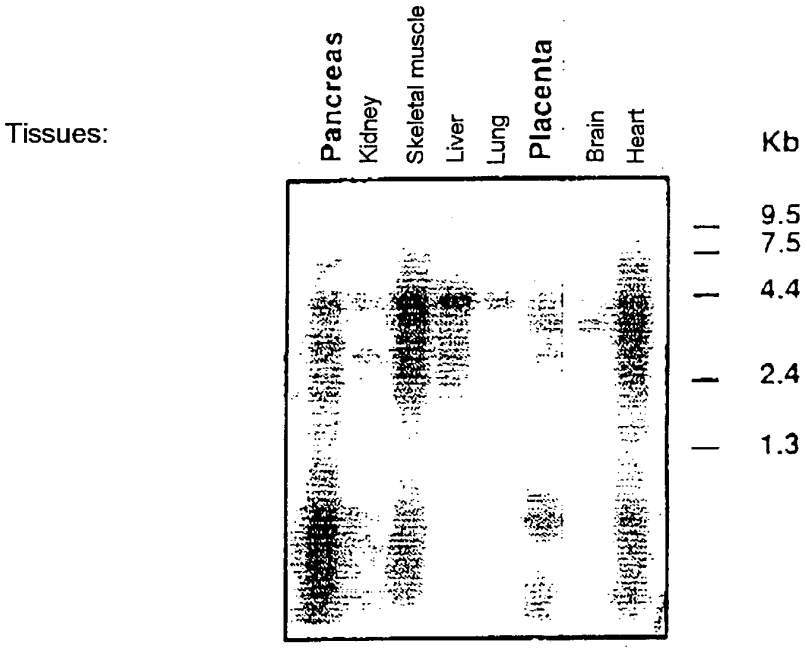


Figure 9

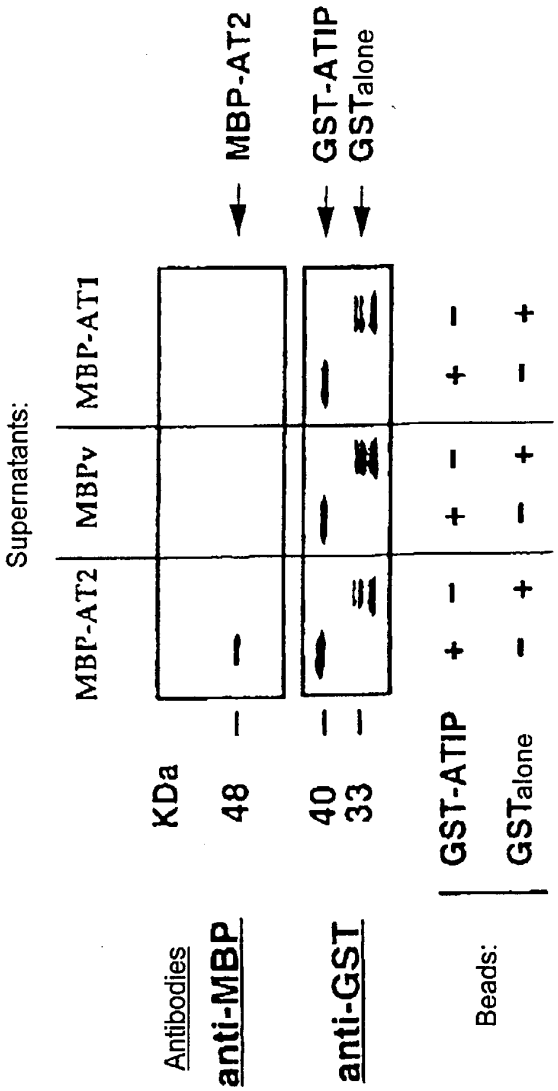

Supernatants:
MBP-AT2
MBPv
MBP-AT1
MBP-AT2
GST-ATIP
GSTalone
KDa
48
40
33
Antibodies
anti-MBP
anti-GST
Beads:
GST-ATIP
GSTalone

Figure 10

Declaration and Power of Attorney for Patent Application
Déclaration et Pouvoirs pour Demande de Brevet
French Language Declaration

En tant l'inventeur nommé ci-après, je déclare par le présent acte que :

As a below named inventor, I hereby declare that :

Mon domicile, mon adresse postale et ma nationalité sont ceux figurant ci-dessous à côté de mon nom.

My residence, post office address and citizenship are as stated next to my name.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed an for which a patent is sought on the invention entitled

Nucleic sequences coding for an AT2 interacting protein interacting with the AT2 receptor and their applications

et dont la description est fournie ci-joint à moins

the specification of which :

☐ ci-joint

☐ a été déposée le

sous le numéro de demande des Etats-Unis ou le numéro de demande international PCT

et modifiée le

(le cas échéant).

☐ is attached hereto.

☒ was filed on

as United States Application Number or PCT International Application Number.
PCT/FR99/01908 filed on August 2, 1999

and was amended on

(if applicable).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait références ci-dessus.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations,§ 1.56.

French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign application(s)
Demande(s) de brevet antérieure(s) dans un autre pays.

(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	Priority claimed Droit de priorité revendiqué ☒ Yes Oui	☐ No Non
FR 98 08600	FRANCE	August 4, 1998		
(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	☐ Yes Oui	☐ No Non

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365© du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande :

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)
(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)

Je déclare que par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique ;et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la section 1001 du Titre 18 du Code de Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hebery declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

French Language Declaration

POUVOIRS : En tant que l'inventeur cité, je désigne par la présente l'(les) avocats(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marquees : (mentionner le nom et le numéro d'enregistrement).

POWER OF ATTORNEY : As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to persecute this application and transact all bussinecs in the Patent and Trademark Office connected therewith : (list name and registration number)

All practitioners associated with
CUSTOMER NUMBER 000826

RAYMOND O. LINKER, JR. Registration No. 26,419

Adresser toute correspondance à :

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CHARLOTTE, NC 28280-4000 U.S.A.

Adresser tout appel téléphonique à :
(nom et numéro de téléphone)

Direct Telephone calls to : (name and telephone number)

(704) 444-1000

100

Nom complete de l'unique ou premier inventeur **ELBAZ Nathalie**	Full name of sole or first inventor
Signature de l'inventeur Date 11.04.01	Inventor's signature Date
Domicile 93170 BAGNOLET (FRANCE) FRX	Residence
Nationalité Française	Citizenship
Adresse Postale 7, Passage des Italiens 93170 BAGNOLET FRANCE	Post Office Address
Nom complete du second co-inventeur, le cas echeant **NAHMIAS Clara**	Full name of second joint inventor, if any
Signature de l'inventeur Date 6/04/01	Second inventor's signature Date
Domicile 75003 Paris (FRANCE) FRX	Residence
Nationalité Française	Citizenship
Adresse Postale ~~4, Rue Bailly 75003 PARIS FRANCE~~ 45 rue de Turenne - 75003 Paris	Post Office Address

200

(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Suppply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

Nom complete du troisième co-inventeur, le cas échéant **STROSBERG Arthur, Donny**	Full name of third joint inventor, if any
Signature de l'inventeur Date	Third inventor's signature Date
Domicile 75015 Paris (FRANCE)	Residence
Nationalité Française	Citizenship
Adresse Postale 66, Rue de Javel 75015 PARIS FRANCE	Post Office Address
Nom complete du quatrième co-inventeur, le cas echeant	Full name of fourth joint inventor, if any
Signature de l'inventeur Date	Fourth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du cinquième co-inventeur, le cas echeant	Full name of fifth joint inventor, if any
Signature de l'inventeur Date	Fifth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du sixième co-inventeur, le cas echeant	Full name of sixth joint inventor, if any
Signature de l'inventeur Date	Sixth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address

(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

Supply similar information and signature for third and subsequent joint inventors.)

SEQUENCE LISTING

<110> Elbaz, Nathalie
Nahmias, Clara
Strosberg, Arthur Donny

<120> NUCLEIC SEQUENCES ENCODING AN AT2
RECEPTOR-INTERACTING PROTEIN (ATIP) AND THEIR APPLICATIONS

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<140> US 09/762,194
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Met
1

ctg ttg tct ccc aaa ttc tcc tta tcc acc atc cac gtc cgc cta acc 228
Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu Thr
5 10 15

gcc aaa gga ctg ctt cga aac ctc cgg ctt cct tcg ggg ctc agg aaa 276
Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg Lys
20 25 30

aac act gtc att ttc cac aca gtt gaa aag ggc agg cag aag aat ccc 324
Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn Pro

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 50                  55                  60                  65

gag aga acg ctt gag ttg gcc caa tac aag aca aaa tgt gaa agc caa      420
Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser Gln
                 70                  75                  80

agt gga ttc atc ctg cac ctc agg cag ctt ctt tcc cgt ggt aac aac      468
Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn Asn
             85                  90                  95

aag ttt gaa gcg ctg aca gtt gtg atc cag cac ctc ctg tct gag cgg      516
Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu Arg
        100                 105                 110

gag gaa gca ctg aag caa cac aaa acc ctc tct caa gaa ctt gtc agc      564
Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val Ser
    115                 120                 125

ctc cgg gga gag cta gtt gct gct tca agc gcc tgt gag aag cta gaa      612
Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu Glu
130                 135                 140                 145

aag gct agg gct gac tta cag aca gcg tat caa gaa ttt gtc cag aaa      660
Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln Lys
                150                 155                 160

cta aac cag cag cat cag aca gac cgg acg gaa ctg gag aac cgg ctg      708
Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg Leu
            165                 170                 175

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Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr Ile
        180                 185                 190

gag gag gca gaa aaa tat aaa act caa ctg caa gag cag ttt gac aac      804
Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp Asn
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Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser His
210                 215                 220                 225

tcg gag aag gtg gaa ttg ctg aag aag acc tat gaa acc tcc ctt tca      900
Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu Ser
                230                 235                 240

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Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp Leu
            245                 250                 255
```

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Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys
        260                 265                 270

agt gaa aac gat gct tta aac gaa agg ttg aaa tca gag gag caa aag     1044
Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln Lys
    275                 280                 285

caa ctg tca aga gag aag gcg aat tcc aaa aac cct cag gtc atg tat     1092
Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met Tyr
290                 295                 300                 305

ctg gag caa gaa cta gaa agc ctg aag gct gtg tta gag atc aag aat     1140
Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn
                310                 315                 320

gag aag ctg cac cag cag gac atg aag cta atg aag atg gaa aag ctg     1188
Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys Leu
            325                 330                 335

gtg gac aat aac aca gca ttg gtt gac aag ctg aag cga ttc cag cag     1236
Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln
        340                 345                 350

gaa aac gag gag tta aaa gct cgc atg gac aaa cac atg gca att tca     1284
Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile Ser
    355                 360                 365

agg caa ctt tcc acc gag cag gcc gcg ctg caa gag tcc ctt gag aag     1332
Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu Lys
370                 375                 380                 385

gag tca aag gtc aac aag aga ctg tcc atg gag aac gag gaa ctt ctg     1380
Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu
                390                 395                 400

tgg aaa ctg cac aac gga gac ctg tgc agc ccc aag aga tcc ccc acc     1428
Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr
            405                 410                 415

tcc tcg gcc atc cct ttc cag tcc ccc agg aat tct ggt tcc ttc tcc     1476
Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe Ser
        420                 425                 430

agc ccc agc atc tca ccc aga tga cggcttctga acgcaggaga ctctctgaag    1530
Ser Pro Ser Ile Ser Pro Arg  *
    435                 440

gcactgaggt gcgcttctgc aggactgacc ctctcatggg aactcgagtt gctgcgttag   1590
ctctctggaa tatccccagg atatcgggag agcagccgcc aaccgtatca gctacgtacg   1650
aatagagagc tccaatagaa gacttttaac ttggtccaaa agcctcctcc aaaaacagat   1710
ttcggaactg aagtggacat agttgcacaa agcacttacg gaacgaggga accttgttct   1770
```

ttgccttcct tcacctaagc ataggctttc cag 1803

<210> 2
<211> 440
<212> PRT
<213> Mus musculus

<400> 2

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Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
 1               5                  10                  15
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
            20                  25                  30
Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
        35                  40                  45
Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
    50                  55                  60
Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
65                  70                  75                  80
Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                85                  90                  95
Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125
Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140
Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160
Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
                165                 170                 175
Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
            180                 185                 190
Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
        195                 200                 205
Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
    210                 215                 220
His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225                 230                 235                 240
Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
                245                 250                 255
Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
            260                 265                 270
Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
        275                 280                 285
Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
    290                 295                 300
Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305                 310                 315                 320
Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
                325                 330                 335
Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
            340                 345                 350
Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
```

```
        355                 360                 365
Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
    370                 375                 380
Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385                 390                 395                 400
Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
                405                 410                 415
Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
            420                 425                 430
Ser Ser Pro Ser Ile Ser Pro Arg
        435                 440
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<210> 3
<211> 1323
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)...(1323)

<400> 3

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atg ctg ttg tct ccc aaa ttc tcc tta tcc acc atc cac gtc cgc cta       48
Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
 1               5                  10                  15

acc gcc aaa gga ctg ctt cga aac ctc cgg ctt cct tcg ggg ctc agg       96
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
            20                  25                  30

aaa aac act gtc att ttc cac aca gtt gaa aag ggc agg cag aag aat      144
Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
        35                  40                  45

ccc agg agc ctg tgc atc cag acc cag aca gct cca gat gtg ctg tcc      192
Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
    50                  55                  60

tcc gag aga acg ctt gag ttg gcc caa tac aag aca aaa tgt gaa agc      240
Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
65                  70                  75                  80

caa agt gga ttc atc ctg cac ctc agg cag ctt ctt tcc cgt ggt aac      288
Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                85                  90                  95

aac aag ttt gaa gcg ctg aca gtt gtg atc cag cac ctc ctg tct gag      336
Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110

cgg gag gaa gca ctg aag caa cac aaa acc ctc tct caa gaa ctt gtc      384
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125
```

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agc ctc cgg gga gag cta gtt gct gct tca agc gcc tgt gag aag cta      432
Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140

gaa aag gct agg gct gac tta cag aca gcg tat caa gaa ttt gtc cag      480
Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160

aaa cta aac cag cag cat cag aca gac cgg acg gaa ctg gag aac cgg      528
Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
                165                 170                 175

ctg aag gac tta tac acc gca gag tgt gag aag ctt cag agc att tac      576
Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
            180                 185                 190

att gag gag gca gaa aaa tat aaa act caa ctg caa gag cag ttt gac      624
Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
        195                 200                 205

aac tta aac gcc gcc cat gag acc act aag ctt gag att gaa gct agc      672
Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
    210                 215                 220

cac tcg gag aag gtg gaa ttg ctg aag aag acc tat gaa acc tcc ctt      720
His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225                 230                 235                 240

tca gaa atc aag aag agc cat gag atg gag aag aag tca ctg gag gat      768
Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
                245                 250                 255

ctg ctt aat gag aag cag gaa tcg ctg gag aaa caa atc aat gat ctg      816
Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
            260                 265                 270

aag agt gaa aac gat gct tta aac gaa agg ttg aaa tca gag gag caa      864
Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
        275                 280                 285

aag caa ctg tca aga gag aag gcg aat tcc aaa aac cct cag gtc atg      912
Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
    290                 295                 300

tat ctg gag caa gaa cta gaa agc ctg aag gct gtg tta gag atc aag      960
Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305                 310                 315                 320

aat gag aag ctg cac cag cag gac atg aag cta atg aag atg gaa aag     1008
Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
                325                 330                 335
```

```
ctg gtg gac aat aac aca gca ttg gtt gac aag ctg aag cga ttc cag     1056
Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
            340                 345                 350

cag gaa aac gag gag tta aaa gct cgc atg gac aaa cac atg gca att     1104
Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
        355                 360                 365

tca agg caa ctt tcc acc gag cag gcc gcg ctg caa gag tcc ctt gag     1152
Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
    370                 375                 380

aag gag tca aag gtc aac aag aga ctg tcc atg gag aac gag gaa ctt     1200
Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385                 390                 395                 400

ctg tgg aaa ctg cac aac gga gac ctg tgc agc ccc aag aga tcc ccc     1248
Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
                405                 410                 415

acc tcc tcg gcc atc cct ttc cag tcc ccc agg aat tct ggt tcc ttc     1296
Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
            420                 425                 430

tcc agc ccc agc atc tca ccc aga tga                                1323
Ser Ser Pro Ser Ile Ser Pro Arg  *
        435                 440
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<210> 4
<211> 440
<212> PRT
<213> Mus musculus

<400> 4

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Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
 1               5                  10                  15
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
            20                  25                  30
Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
        35                  40                  45
Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
    50                  55                  60
Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
65                  70                  75                  80
Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                85                  90                  95
Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125
Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140
```

```
Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160
Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
                165                 170                 175
Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
            180                 185                 190
Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
        195                 200                 205
Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
    210                 215                 220
His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225                 230                 235                 240
Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
                245                 250                 255
Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
            260                 265                 270
Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
        275                 280                 285
Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
    290                 295                 300
Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305                 310                 315                 320
Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
                325                 330                 335
Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
            340                 345                 350
Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
        355                 360                 365
Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
    370                 375                 380
Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385                 390                 395                 400
Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
                405                 410                 415
Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
            420                 425                 430
Ser Ser Pro Ser Ile Ser Pro Arg
        435                 440
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<210> 5
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)...(354)
<223> Insert identified by two-hybrid screening of a M. musculus foetal cDNA library

<223> Insert identified by two-hybrid screening of a M. musculus foetal cDNA library

<400> 5
cat cag aca gac cgg acg gaa ctg gag aac cgg ctg aag gac tta tac 48
His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg Leu Lys Asp Leu Tyr
1 5 10 15

acc gca gag tgt gag aag ctt cag agc att tac att gag gag gca gaa 96
Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr Ile Glu Glu Ala Glu
20 25 30

aaa tat aaa act caa ctg caa gag cag ttt gac aac tta aac gcc gcc 144
Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala Ala
35 40 45

cat gag acc act aag ctt gag att gaa gct agc cac tcg gag aag gtg 192
His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Val
50 55 60

gaa ttg ctg aag aag acc tat gaa acc tcc ctt tca gaa atc aag aag 240
Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu Ser Glu Ile Lys Lys
65 70 75 80

agc cat gag atg gag aag aag tca ctg gag gat ctg ctt aat gag aag 288
Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp Leu Leu Asn Glu Lys
85 90 95

cag gaa tcg ctg gag aaa caa atc aat gat ctg aag agt gaa aac gat 336
Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
100 105 110

gct tta aac gaa agg ttg 354
Ala Leu Asn Glu Arg Leu
115

<210> 6
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Insert identified by yeast two hybrid screening of
a M. musculus fetal cDNA library

<400> 6
His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg Leu Lys Asp Leu Tyr
1 5 10 15
Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr Ile Glu Glu Ala Glu
20 25 30
Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala Ala
35 40 45
His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Val
50 55 60
Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu Ser Glu Ile Lys Lys

```
65                  70                  75                  80
Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp Leu Leu Asn Glu Lys
                85                  90                  95
Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            100                 105                 110
Ala Leu Asn Glu Arg Leu
        115
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<210> 7
<211> 3742
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (293)...(1600)

<400> 7

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cagtgtgatg tggttcagag gcagcttcta gacctgcagg agggagattg tattcagagg     60
aagagcatca ttttggcaac atctgaaagt gaaaacggaa gccagaaaca cttggccagc    120
cctgggggat ttttttcttc tatgcctctg tggtggaatg acatttgctg tgtaggcatc    180
tttcctctga ctgtatttct tggccttgaa gagtactgag tttaaaaaga cagtatgtga    240
cagtccatgg aaattgcctc ttctgtgaaa tctcgccacc tgctccgaag ac atg ttg    298
                                                          Met Leu
                                                           1

ttg tct ccc aaa ttc tcc tta tcc acc att cac ata cga ctg acg gcc      346
Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Ile Arg Leu Thr Ala
         5                  10                  15

aaa gga ttg ctt cga aac ctt cga ctt cct tca ggg ttt agg aga agc      394
Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Phe Arg Arg Ser
     20                  25                  30

act gtt gtt ttc cac aca gtt gaa aag agc agg caa aag aat cct cga      442
Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn Pro Arg
 35                  40                  45                  50

agc tta tgt atc cag cca cag aca gct ccc gat gcg ctg ccc cct gag      490
Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro Pro Glu
                 55                  60                  65

aaa aca ctt gaa ttg acg caa tat aaa aca aaa tgt gaa aac caa agt      538
Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn Gln Ser
             70                  75                  80

gga ttt atc ctg cag ctc aag cag ctt ctt gcc tgt ggt aat acc aag      586
Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn Thr Lys
         85                  90                  95

ttt gag gca ttg aca gtt gtg att cag cac ctg ctg tct gag cgg gag      634
Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu Arg Glu
    100                 105                 110
```

```
gaa gca ctg aaa caa cac aaa acc cta tct caa gaa ctt gtt aac ctc      682
Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val Asn Leu
115                 120                 125                 130

cgg gga gag cta gtc act gct tca acc acc tgt gag aaa tta gaa aaa      730
Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu Glu Lys
                135                 140                 145

gcc agg aat gag tta caa aca gtg tat gaa gca ttc gtc cag cag cac      778
Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln Gln His
            150                 155                 160

cag gct gaa aaa aca gaa cga gag aat cgg ctt aaa gag ttt tac acc      826
Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe Tyr Thr
        165                 170                 175

agg gag tat gaa aag ctt cgg gac act tac att gaa gaa gca gag aag      874
Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala Glu Lys
    180                 185                 190

tac aaa atg caa ttg caa gag cag ttt gac aac tta aat gcg cat gaa      922
Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala His Glu
195                 200                 205                 210

acc tct aag ttg gaa att gaa gct agc cac tca gag aaa ctt gaa ttg      970
Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu Glu Leu
                215                 220                 225

cta aag aag gcc tat gaa gcc tcc ctt tca gaa att aag aaa ggc cat     1018
Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys Gly His
            230                 235                 240

gaa ata gaa aag aaa tcg ctt gaa gat tta ctt tct gag aag cag gaa     1066
Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys Gln Glu
        245                 250                 255

tcg cta gag aag caa atc aat gat ctg aag agt gaa aat gat gct tta     1114
Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp Ala Leu
    260                 265                 270

aat gaa aaa ttg aaa tca gaa gaa caa aaa aga aga gca aga gaa aaa     1162
Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg Glu Lys
275                 280                 285                 290

gca aat ttg aaa aat cct cag atc atg tat cta gaa cag gag tta gaa     1210
Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu Leu Glu
                295                 300                 305

agc ctg aaa gct gtg tta gag atc aag aat gag aaa ctg cat caa cag     1258
Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His Gln Gln
            310                 315                 320
```

```
gac atc aag tta atg aaa atg gag aaa ctg gtg gac aac aac aca gca     1306
Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn Thr Ala
        325                 330                 335

ttg gtt gac aaa ttg aag cgt ttc cag cag gag aat gaa gaa ttg aaa     1354
Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu Leu Lys
    340                 345                 350

gct cgg atg gac aag cac atg gca atc tca agg cag ctt tcc acg gag     1402
Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser Thr Glu
355                 360                 365                 370

cag gct gtt ctg caa gag tcg ctg gag aag gag tcg aaa gtc aac aag     1450
Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val Asn Lys
                375                 380                 385

cga ctc tct atg gaa aac gag gag ctt ctg tgg aaa ctg cac aat ggg     1498
Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His Asn Gly
            390                 395                 400

gac ctg tgt agc ccc aag aga tcc ccc aca tcc tcc gcc atc cct ttg     1546
Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile Pro Leu
        405                 410                 415

cag tca cca agg aat tcg ggc tcc ttc cct agc ccc agc att tca ccc     1594
Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile Ser Pro
    420                 425                 430

aga tga cacgtcccca aagtccacag actctctgaa agcattttga tgcaggtctg      1650
Arg  *
435

caggactgac cccaaggagg aacgtgggca caagaggtat atcagcacac gtgtgatcac   1710
cgtaggtaac tggagcgtca ccaccggcgg aatcgagctt ctgagactgg aagtctggag   1770
gaagactttt gcctccgtcc aaaagattcc tccaaaaaaa gatttaaaaa aagatttcgg   1830
catcgacacg gacgttgttg cacaaagcac ttaaagaacg agagcatctt gttcattgcc   1890
tttttcacct aagcataagg ggaaaaactc tcagggccct attaagattt ataacctttg   1950
taatgttctt caccacagac accttcttgt gagttttcag tctgactgtg ggggtggggg   2010
gtgtgaatga aatggatgtc acagagtgtc atgtgtctga tgcagcctcc tctgctgtgt   2070
attaaatgtc aaaatctgaa tatatctgga tatgtactaa tcaaataata atcaatcaat   2130
cagcatatac atttcagcca aagccataga agaaaaagca atagttgctt gaattatgat   2190
catctaccac caactctgct cagccctgta acagggtagg gagagggtat aacaggaaga   2250
gctttgactt gtccctgtct atacattctc tgtatctttt gggggtaact tcttggcagt   2310
ttttcagtgt tcagccatgt cagttgaaac tagatttttc tgtagatttt ttacttaccc   2370
atgtgagcct aacactatcc tgtaattcat tttctcaggc tatgtgtaaa tgtagaaccc   2430
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aatgggtttt tccaccttat ttttaccttt gatctaccct tgcagattta acctgtcttc   2550
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gagccccaga gccagctcat cttccaggtg ctgaaaccac tttccaaata aactaaagcc   2730
tggatttgat attacaaatt ttgggaaatc ttagaataaa gaacgagaac aaggaagtca   2790
ttggctagta taattaagaa aggtaggatt cagtgcttac cgatgatgca gtacttgata   2850
gaagaaaaca gtctgggagg atagcgctca tttttcagtt acccttaag gagtcccttt    2910
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gtctttggga aagtagcaga atggtccgct tctttcccat gagtggaaaa tgtggcttgt   2970
ccaactctcc tccaggttgc atttcagttt ctttccaaaa cttattacct cccctaatcc   3030
tgagactttg gaaaaggtgg aaggaagaac tgttgcttta tctccccctc cctgcatgtg   3090
tcaacattgt gatgtcagta tttactaatc tacattcagt ggctgtacaa ataacagctg   3150
tagtaagaag agattcagga tgctagaggt gaatatttgg gtcatttaca tgtacactac   3210
atagcaagtt gatactcatg ttgcatgttc ttttaaatta gtgattttgt gtcttaagtc   3270
tttaacttcc aatacttcat catgtatgta accttccatg tttgcttctg ataaatggaa   3330
atgtaggttc actgccactt catgagatat ctctgctcac gcttccaagt tgttctcaat   3390
gacattagcc aaagttgggt ttgccattca tcccctaggc atggtaaatc ttgtgttgtt   3450
ccctgctgtc ctccgtatta cgtgaccggc aaataaatct catagcagtt aatataaaac   3510
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gattttgttt aaaccaaatg tttcatgtag aatgcaaaat gttggcacgt caaaaatatg   3630
aatgtgtaga caactgtagt tgtgctcagt ttgtagtgat gggaagtgta ttttactctg   3690
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<210> 8
<211> 435
<212> PRT
<213> Homo sapiens

<400> 8

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 1               5                  10                  15
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Phe Arg
            20                  25                  30
Arg Ser Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn
        35                  40                  45
Pro Arg Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro
    50                  55                  60
Pro Glu Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn
65                  70                  75                  80
Gln Ser Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn
                85                  90                  95
Thr Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125
Asn Leu Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu
    130                 135                 140
Glu Lys Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln
145                 150                 155                 160
Gln His Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe
                165                 170                 175
Tyr Thr Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala
            180                 185                 190
Glu Lys Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala
        195                 200                 205
His Glu Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu
    210                 215                 220
Glu Leu Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys
225                 230                 235                 240
Gly His Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys
                245                 250                 255
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Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            260                 265                 270
Ala Leu Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg
        275                 280                 285
Glu Lys Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu
    290                 295                 300
Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His
305                 310                 315                 320
Gln Gln Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn
                325                 330                 335
Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu
            340                 345                 350
Leu Lys Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser
        355                 360                 365
Thr Glu Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val
    370                 375                 380
Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His
385                 390                 395                 400
Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile
                405                 410                 415
Pro Leu Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile
            420                 425                 430
Ser Pro Arg
        435
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<210> 9
<211> 1308
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1308)

<400> 9

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 1               5                  10                  15

acg gcc aaa gga ttg ctt cga aac ctt cga ctt cct tca ggg ttt agg       96
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Phe Arg
             20                  25                  30

aga agc act gtt gtt ttc cac aca gtt gaa aag agc agg caa aag aat      144
Arg Ser Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn
         35                  40                  45

cct cga agc tta tgt atc cag cca cag aca gct ccc gat gcg ctg ccc      192
Pro Arg Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro
     50                  55                  60

cct gag aaa aca ctt gaa ttg acg caa tat aaa aca aaa tgt gaa aac      240
Pro Glu Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn
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65                  70                  75                  80

caa agt gga ttt atc ctg cag ctc aag cag ctt ctt gcc tgt ggt aat      288
Gln Ser Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn
                 85                  90                  95

acc aag ttt gag gca ttg aca gtt gtg att cag cac ctg ctg tct gag      336
Thr Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110

cgg gag gaa gca ctg aaa caa cac aaa acc cta tct caa gaa ctt gtt      384
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125

aac ctc cgg gga gag cta gtc act gct tca acc acc tgt gag aaa tta      432
Asn Leu Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu
    130                 135                 140

gaa aaa gcc agg aat gag tta caa aca gtg tat gaa gca ttc gtc cag      480
Glu Lys Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln
145                 150                 155                 160

cag cac cag gct gaa aaa aca gaa cga gag aat cgg ctt aaa gag ttt      528
Gln His Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe
                165                 170                 175

tac acc agg gag tat gaa aag ctt cgg gac act tac att gaa gaa gca      576
Tyr Thr Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala
            180                 185                 190

gag aag tac aaa atg caa ttg caa gag cag ttt gac aac tta aat gcg      624
Glu Lys Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala
        195                 200                 205

cat gaa acc tct aag ttg gaa att gaa gct agc cac tca gag aaa ctt      672
His Glu Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu
    210                 215                 220

gaa ttg cta aag aag gcc tat gaa gcc tcc ctt tca gaa att aag aaa      720
Glu Leu Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys
225                 230                 235                 240

ggc cat gaa ata gaa aag aaa tcg ctt gaa gat tta ctt tct gag aag      768
Gly His Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys
                245                 250                 255

cag gaa tcg cta gag aag caa atc aat gat ctg aag agt gaa aat gat      816
Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            260                 265                 270

gct tta aat gaa aaa ttg aaa tca gaa gaa caa aaa aga aga gca aga      864
Ala Leu Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg
        275                 280                 285
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gaa aaa gca aat ttg aaa aat cct cag atc atg tat cta gaa cag gag      912
Glu Lys Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu
    290                 295                 300

tta gaa agc ctg aaa gct gtg tta gag atc aag aat gag aaa ctg cat      960
Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His
305                 310                 315                 320

caa cag gac atc aag tta atg aaa atg gag aaa ctg gtg gac aac aac     1008
Gln Gln Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn
                325                 330                 335

aca gca ttg gtt gac aaa ttg aag cgt ttc cag cag gag aat gaa gaa     1056
Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu
            340                 345                 350

ttg aaa gct cgg atg gac aag cac atg gca atc tca agg cag ctt tcc     1104
Leu Lys Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser
        355                 360                 365

acg gag cag gct gtt ctg caa gag tcg ctg gag aag gag tcg aaa gtc     1152
Thr Glu Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val
    370                 375                 380

aac aag cga ctc tct atg gaa aac gag gag ctt ctg tgg aaa ctg cac     1200
Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His
385                 390                 395                 400

aat ggg gac ctg tgt agc ccc aag aga tcc ccc aca tcc tcc gcc atc     1248
Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile
                405                 410                 415

cct ttg cag tca cca agg aat tcg ggc tcc ttc cct agc ccc agc att     1296
Pro Leu Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile
            420                 425                 430

tca ccc aga tga                                                    1308
Ser Pro Arg  *
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<210> 10
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<212> PRT
<213> Homo sapiens

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            20                  25                  30
Arg Ser Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn
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        35                  40                  45
Pro Arg Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro
    50                  55                  60
Pro Glu Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn
65                  70                  75                  80
Gln Ser Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn
                85                  90                  95
Thr Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125
Asn Leu Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu
    130                 135                 140
Glu Lys Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln
145                 150                 155                 160
Gln His Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe
                165                 170                 175
Tyr Thr Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala
            180                 185                 190
Glu Lys Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala
        195                 200                 205
His Glu Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu
    210                 215                 220
Glu Leu Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys
225                 230                 235                 240
Gly His Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys
                245                 250                 255
Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            260                 265                 270
Ala Leu Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg
        275                 280                 285
Glu Lys Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu
    290                 295                 300
Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His
305                 310                 315                 320
Gln Gln Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn
                325                 330                 335
Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu
            340                 345                 350
Leu Lys Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser
        355                 360                 365
Thr Glu Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val
    370                 375                 380
Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His
385                 390                 395                 400
Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile
                405                 410                 415
Pro Leu Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile
            420                 425                 430
Ser Pro Arg
        435
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<210> 11

<211> 33
<212> DNA
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<220>
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<212> DNA
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<220>
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<400> 12
ccggaattca ctacaacctt tcgtttaaag catc 34

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE-CNRS
(B) STREET: 3 rue Michel-Ange
(C) :CITY: Paris
(E) COUNTRY: FRANCE
(F) POSTAL CODE: 75794 PARIS Cedex 16

(A) NAME: ELBAZ Nathalie
(B) STREET: 7 Passage des Italiens
(C) CITY: Bagnolet
(E) COUNTRY: FRANCE
(F) POSTAL CODE: 93170

(A) NAME: NAHMIAS Clara
(B) STREET: 4 rue Bailly
(C) CITY: Paris
(E) COUNTRY: FRANCE
(F) POSTAL CODE: 75003

(A) NAME: STROSBERG Arthur Donny
(B) STREET: 66 rue de Javel
(C) CITY: Paris
(E) COUNTRY: FRANCE
(F) POSTAL CODE: 75015

(ii) TITLE OF THE INVENTION: NUCLEIC SEQUENCES ENCODING AN AT2 RECEPTOR-INTERACTING PROTEIN (ATIP) AND THEIR APPLICATIONS

(iii) NUMBER OF SEQUENCES: 12

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1803 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION:178..1500

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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TGATGGTCCC TGGAAAAGCT GCTTCCCCTG CGAAGTTCTC CCACTGGCTT CGAAGAC        177

ATG CTG TTG TCT CCC AAA TTC TCC TTA TCC ACC ATC CAC GTC CGC CTA        225
Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
  1               5                  10                  15

ACC GCC AAA GGA CTG CTT CGA AAC CTC CGG CTT CCT TCG GGG CTC AGG        273
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
             20                  25                  30

AAA AAC ACT GTC ATT TTC CAC ACA GTT GAA AAG GGC AGG CAG AAG AAT        321
Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
         35                  40                  45

CCC AGG AGC CTG TGC ATC CAG ACC CAG ACA GCT CCA GAT GTG CTG TCC        369
Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
     50                  55                  60

TCC GAG AGA ACG CTT GAG TTG GCC CAA TAC AAG ACA AAA TGT GAA AGC        417
Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
 65                  70                  75                  80

CAA AGT GGA TTC ATC CTG CAC CTC AGG CAG CTT CTT TCC CGT GGT AAC        465
Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                 85                  90                  95

AAC AAG TTT GAA GCG CTG ACA GTT GTG ATC CAG CAC CTC CTG TCT GAG        513
Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110

CGG GAG GAA GCA CTG AAG CAA CAC AAA ACC CTC TCT CAA GAA CTT GTC        561
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125

AGC CTC CGG GGA GAG CTA GTT GCT GCT TCA AGC GCC TGT GAG AAG CTA        609
Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140

GAA AAG GCT AGG GCT GAC TTA CAG ACA GCG TAT CAA GAA TTT GTC CAG        657
Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160

AAA CTA AAC CAG CAG CAT CAG ACA GAC CGG ACG GAA CTG GAG AAC CGG        705
Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
                165                 170                 175

CTG AAG GAC TTA TAC ACC GCA GAG TGT GAG AAG CTT CAG AGC ATT TAC        753
Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
            180                 185                 190
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ATT GAG GAG GCA GAA AAA TAT AAA ACT CAA CTG CAA GAG CAG TTT GAC        801
Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
        195                 200                 205

AAC TTA AAC GCC GCC CAT GAG ACC ACT AAG CTT GAG ATT GAA GCT AGC        849
Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
    210                 215                 220

CAC TCG GAG AAG GTG GAA TTG CTG AAG AAG ACC TAT GAA ACC TCC CTT        897
His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225                 230                 235                 240

TCA GAA ATC AAG AAG AGC CAT GAG ATG GAG AAG AAG TCA CTG GAG GAT        945
Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
                245                 250                 255

CTG CTT AAT GAG AAG CAG GAA TCG CTG GAG AAA CAA ATC AAT GAT CTG        993
Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
            260                 265                 270

AAG AGT GAA AAC GAT GCT TTA AAC GAA AGG TTG AAA TCA GAG GAG CAA       1041
Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
        275                 280                 285

AAG CAA CTG TCA AGA GAG AAG GCG AAT TCC AAA AAC CCT CAG GTC ATG       1089
Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
    290                 295                 300

TAT CTG GAG CAA GAA CTA GAA AGC CTG AAG GCT GTG TTA GAG ATC AAG       1137
Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305                 310                 315                 320

AAT GAG AAG CTG CAC CAG CAG GAC ATG AAG CTA ATG AAG ATG GAA AAG       1185
Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
                325                 330                 335

CTG GTG GAC AAT AAC ACA GCA TTG GTT GAC AAG CTG AAG CGA TTC CAG       1233
Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
            340                 345                 350

CAG GAA AAC GAG GAG TTA AAA GCT CGC ATG GAC AAA CAC ATG GCA ATT       1281
Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
        355                 360                 365

TCA AGG CAA CTT TCC ACC GAG CAG GCC GCG CTG CAA GAG TCC CTT GAG       1329
Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
    370                 375                 380

AAG GAG TCA AAG GTC AAC AAG AGA CTG TCC ATG GAG AAC GAG GAA CTT       1377
Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385                 390                 395                 400

CTG TGG AAA CTG CAC AAC GGA GAC CTG TGC AGC CCC AAG AGA TCC CCC       1425
Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
                405                 410                 415
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ACC TCC TCG GCC ATC CCT TTC CAG TCC CCC AGG AAT TCT GGT TCC TTC      1473
Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
            420                 425                 430

TCC AGC CCC AGC ATC TCA CCC AGA TGA CGGCTTCTGA ACGCAGGAGA           1520
Ser Ser Pro Ser Ile Ser Pro Arg  *
        435                 440

CTCTCTGAAG GCACTGAGGT GCGCTTCTGC AGGACTGACC CTCTCATGGG AACTCGAGTT   1580

GCTGCGTTAG CTCTCTGGAA TATCCCCAGG ATATCGGGAG AGCAGCCGCC AACCGTATCA   1640

GCTACGTACG AATAGAGAGC TCCAATAGAA GACTTTTAAC TTGGTCCAAA AGCCTCCTCC   1700

AAAAACAGAT TTCGGAACTG AAGTGGACAT AGTTGCACAA AGCACTTACG GAACGAGGGA   1760

ACCTTGTTCT TTGCCTTCCT TCACCTAAGC ATAGGCTTTC CAG                     1803
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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 440 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
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Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
            20                  25                  30

Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
        35                  40                  45

Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
    50                  55                  60

Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
65                  70                  75                  80

Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                85                  90                  95

Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110

Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125

Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140
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Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160

Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
                165                 170                 175

Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
            180                 185                 190

Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
        195                 200                 205

Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
    210                 215                 220

His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225                 230                 235                 240

Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
                245                 250                 255

Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
            260                 265                 270

Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
        275                 280                 285

Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
    290                 295                 300

Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305                 310                 315                 320

Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
                325                 330                 335

Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
            340                 345                 350

Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
        355                 360                 365

Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
    370                 375                 380

Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385                 390                 395                 400

Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
                405                 410                 415

Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
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Ser Ser Pro Ser Ile Ser Pro Arg  *
        435                 440
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(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1323 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION:1..1322

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
ATG CTG TTG TCT CCC AAA TTC TCC TTA TCC ACC ATC CAC GTC CGC CTA        48
Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
          445                 450                 455

ACC GCC AAA GGA CTG CTT CGA AAC CTC CGG CTT CCT TCG GGG CTC AGG        96
Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
      460                 465                 470

AAA AAC ACT GTC ATT TTC CAC ACA GTT GAA AAG GGC AGG CAG AAG AAT       144
Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn

CCC AGG AGC CTG TGC ATC CAG ACC CAG ACA GCT CCA GAT GTG CTG TCC       192
Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser

TCC GAG AGA ACG CTT GAG TTG GCC CAA TAC AAG ACA AAA TGT GAA AGC       240
Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser

CAA AGT GGA TTC ATC CTG CAC CTC AGG CAG CTT CTT TCC CGT GGT AAC       288
Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn

AAC AAG TTT GAA GCG CTG ACA GTT GTG ATC CAG CAC CTC CTG TCT GAG       336
Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu

CGG GAG GAA GCA CTG AAG CAA CAC AAA ACC CTC TCT CAA GAA CTT GTC       384
Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val

AGC CTC CGG GGA GAG CTA GTT GCT GCT TCA AGC GCC TGT GAG AAG CTA       432
Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu

GAA AAG GCT AGG GCT GAC TTA CAG ACA GCG TAT CAA GAA TTT GTC CAG       480
Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
```

```
AAA CTA AAC CAG CAG CAT CAG ACA GAC CGG ACG GAA CTG GAG AAC CGG        528
Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg

CTG AAG GAC TTA TAC ACC GCA GAG TGT GAG AAG CTT CAG AGC ATT TAC        576
Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr

ATT GAG GAG GCA GAA AAA TAT AAA ACT CAA CTG CAA GAG CAG TTT GAC        624
Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp

AAC TTA AAC GCC GCC CAT GAG ACC ACT AAG CTT GAG ATT GAA GCT AGC        672
Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser

CAC TCG GAG AAG GTG GAA TTG CTG AAG AAG ACC TAT GAA ACC TCC CTT        720
His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu

TCA GAA ATC AAG AAG AGC CAT GAG ATG GAG AAG AAG TCA CTG GAG GAT        768
Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp

CTG CTT AAT GAG AAG CAG GAA TCG CTG GAG AAA CAA ATC AAT GAT CTG        816
Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu

AAG AGT GAA AAC GAT GCT TTA AAC GAA AGG TTG AAA TCA GAG GAG CAA        864
Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln

AAG CAA CTG TCA AGA GAG AAG GCG AAT TCC AAA AAC CCT CAG GTC ATG        912
Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met

TAT CTG GAG CAA GAA CTA GAA AGC CTG AAG GCT GTG TTA GAG ATC AAG        960
Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys

AAT GAG AAG CTG CAC CAG CAG GAC ATG AAG CTA ATG AAG ATG GAA AAG       1008
Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys

CTG GTG GAC AAT AAC ACA GCA TTG GTT GAC AAG CTG AAG CGA TTC CAG       1056
Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln

CAG GAA AAC GAG GAG TTA AAA GCT CGC ATG GAC AAA CAC ATG GCA ATT       1104
Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile

TCA AGG CAA CTT TCC ACC GAG CAG GCC GCG CTG CAA GAG TCC CTT GAG       1152
Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
```

```
AAG GAG TCA AAG GTC AAC AAG AGA CTG TCC ATG GAG AAC GAG GAA CTT      1200
Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu

CTG TGG AAA CTG CAC AAC GGA GAC CTG TGC AGC CCC AAG AGA TCC CCC      1248
Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro

ACC TCC TCG GCC ATC CCT TTC CAG TCC CCC AGG AAT TCT GGT TCC TTC      1296
Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe

TCC AGC CCC AGC ATC TCA CCC AGA  TG A                               1323
Ser Ser Pro Ser Ile Ser Pro Arg
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 440 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Val Arg Leu
 1               5                  10                  15

Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Leu Arg
            20                  25                  30

Lys Asn Thr Val Ile Phe His Thr Val Glu Lys Gly Arg Gln Lys Asn
        35                  40                  45

Pro Arg Ser Leu Cys Ile Gln Thr Gln Thr Ala Pro Asp Val Leu Ser
    50                  55                  60

Ser Glu Arg Thr Leu Glu Leu Ala Gln Tyr Lys Thr Lys Cys Glu Ser
65                  70                  75                  80

Gln Ser Gly Phe Ile Leu His Leu Arg Gln Leu Leu Ser Arg Gly Asn
                85                  90                  95

Asn Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
            100                 105                 110

Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
        115                 120                 125

Ser Leu Arg Gly Glu Leu Val Ala Ala Ser Ser Ala Cys Glu Lys Leu
    130                 135                 140

Glu Lys Ala Arg Ala Asp Leu Gln Thr Ala Tyr Gln Glu Phe Val Gln
145                 150                 155                 160
```

Lys Leu Asn Gln Gln His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg
165 170 175

Leu Lys Asp Leu Tyr Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr
180 185 190

Ile Glu Glu Ala Glu Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp
195 200 205

Asn Leu Asn Ala Ala His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser
210 215 220

His Ser Glu Lys Val Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu
225 230 235 240

Ser Glu Ile Lys Lys Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp
245 250 255

Leu Leu Asn Glu Lys Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu
260 265 270

Lys Ser Glu Asn Asp Ala Leu Asn Glu Arg Leu Lys Ser Glu Glu Gln
275 280 285

Lys Gln Leu Ser Arg Glu Lys Ala Asn Ser Lys Asn Pro Gln Val Met
290 295 300

Tyr Leu Glu Gln Glu Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys
305 310 315 320

Asn Glu Lys Leu His Gln Gln Asp Met Lys Leu Met Lys Met Glu Lys
325 330 335

Leu Val Asp Asn Asn Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln
340 345 350

Gln Glu Asn Glu Glu Leu Lys Ala Arg Met Asp Lys His Met Ala Ile
355 360 365

Ser Arg Gln Leu Ser Thr Glu Gln Ala Ala Leu Gln Glu Ser Leu Glu
370 375 380

Lys Glu Ser Lys Val Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu
385 390 395 400

Leu Trp Lys Leu His Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro
405 410 415

Thr Ser Ser Ala Ile Pro Phe Gln Ser Pro Arg Asn Ser Gly Ser Phe
420 425 430

Ser Ser Pro Ser Ile Ser Pro Arg
435 440

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 354 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION:1..354

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
CAT CAG ACA GAC CGG ACG GAA CTG GAG AAC CGG CTG AAG GAC TTA TAC        48
His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg Leu Lys Asp Leu Tyr
            440                 445                 450

ACC GCA GAG TGT GAG AAG CTT CAG AGC ATT TAC ATT GAG GAG GCA GAA        96
Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr Ile Glu Glu Ala Glu
        455                 460                 465

AAA TAT AAA ACT CAA CTG CAA GAG CAG TTT GAC AAC TTA AAC GCC GCC       144
Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala Ala
    470                 475                 480

CAT GAG ACC ACT AAG CTT GAG ATT GAA GCT AGC CAC TCG GAG AAG GTG       192
His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Val
485                 490                 495                 500

GAA TTG CTG AAG AAG ACC TAT GAA ACC TCC CTT TCA GAA ATC AAG AAG       240
Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu Ser Glu Ile Lys Lys
                505                 510                 515

AGC CAT GAG ATG GAG AAG AAG TCA CTG GAG GAT CTG CTT AAT GAG AAG       288
Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp Leu Leu Asn Glu Lys
            520                 525                 530

CAG GAA TCG CTG GAG AAA CAA ATC AAT GAT CTG AAG AGT GAA AAC GAT       336
Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
        535                 540                 545

GCT TTA AAC GAA AGG TTG                                              354
Ala Leu Asn Glu Arg Leu
    550
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 118 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
His Gln Thr Asp Arg Thr Glu Leu Glu Asn Arg Leu Lys Asp Leu Tyr
 1               5                  10                  15

Thr Ala Glu Cys Glu Lys Leu Gln Ser Ile Tyr Ile Glu Glu Ala Glu
            20                  25                  30

Lys Tyr Lys Thr Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala Ala
        35                  40                  45

His Glu Thr Thr Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Val
    50                  55                  60

Glu Leu Leu Lys Lys Thr Tyr Glu Thr Ser Leu Ser Glu Ile Lys Lys
65                  70                  75                  80

Ser His Glu Met Glu Lys Lys Ser Leu Glu Asp Leu Leu Asn Glu Lys
                85                  90                  95

Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            100                 105                 110

Ala Leu Asn Glu Arg Leu
        115
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3742 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION:293..1600

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
CAGTGTGATG TGGTTCAGAG GCAGCTTCTA GACCTGCAGG AGGGAGATTG TATTCAGAGG      60

AAGAGCATCA TTTTGGCAAC ATCTGAAAGT GAAAACGGAA GCCAGAAACA CTTGGCCAGC     120

CCTGGGGGAT TTTTTTCTTC TATGCCTCTG TGGTGGAATG ACATTTGCTG TGTAGGCATC     180

TTTCCTCTGA CTGTATTTCT TGGCCTTGAA GAGTACTGAG TTTAAAAAGA CAGTATGTGA     240

CAGTCCATGG AAATTGCCTC TTCTGTGAAA TCTCGCCACC TGCTCCGAAG AC ATG         295
                                                              Met
```

```
TTG TTG TCT CCC AAA TTC TCC TTA TCC ACC ATT CAC ATA CGA CTG ACG      343
Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Ile Arg Leu Thr

GCC AAA GGA TTG CTT CGA AAC CTT CGA CTT CCT TCA GGG TTT AGG AGA      391
Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Phe Arg Arg

AGC ACT GTT GTT TTC CAC ACA GTT GAA AAG AGC AGG CAA AAG AAT CCT      439
Ser Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn Pro

CGA AGC TTA TGT ATC CAG CCA CAG ACA GCT CCC GAT GCG CTG CCC CCT      487
Arg Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro Pro

GAG AAA ACA CTT GAA TTG ACG CAA TAT AAA ACA AAA TGT GAA AAC CAA      535
Glu Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn Gln

AGT GGA TTT ATC CTG CAG CTC AAG CAG CTT CTT GCC TGT GGT AAT ACC      583
Ser Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn Thr

AAG TTT GAG GCA TTG ACA GTT GTG ATT CAG CAC CTG CTG TCT GAG CGG      631
Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu Arg

GAG GAA GCA CTG AAA CAA CAC AAA ACC CTA TCT CAA GAA CTT GTT AAC      679
Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val Asn

CTC CGG GGA GAG CTA GTC ACT GCT TCA ACC ACC TGT GAG AAA TTA GAA      727
Leu Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu Glu

AAA GCC AGG AAT GAG TTA CAA ACA GTG TAT GAA GCA TTC GTC CAG CAG      775
Lys Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln Gln

CAC CAG GCT GAA AAA ACA GAA CGA GAG AAT CGG CTT AAA GAG TTT TAC      823
His Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe Tyr

ACC AGG GAG TAT GAA AAG CTT CGG GAC ACT TAC ATT GAA GAA GCA GAG      871
Thr Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala Glu

AAG TAC AAA ATG CAA TTG CAA GAG CAG TTT GAC AAC TTA AAT GCG CAT      919
Lys Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala His

GAA ACC TCT AAG TTG GAA ATT GAA GCT AGC CAC TCA GAG AAA CTT GAA      967
Glu Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu Glu

TTG CTA AAG AAG GCC TAT GAA GCC TCC CTT TCA GAA ATT AAG AAA GGC     1015
Leu Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys Gly
```

```
CAT GAA ATA GAA AAG AAA TCG CTT GAA GAT TTA CTT TCT GAG AAG CAG      1063
His Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys Gln

GAA TCG CTA GAG AAG CAA ATC AAT GAT CTG AAG AGT GAA AAT GAT GCT      1111
Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp Ala

TTA AAT GAA AAA TTG AAA TCA GAA GAA CAA AAA AGA AGA GCA AGA GAA      1159
Leu Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg Glu

AAA GCA AAT TTG AAA AAT CCT CAG ATC ATG TAT CTA GAA CAG GAG TTA      1207
Lys Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu Leu

GAA AGC CTG AAA GCT GTG TTA GAG ATC AAG AAT GAG AAA CTG CAT CAA      1255
Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His Gln

CAG GAC ATC AAG TTA ATG AAA ATG GAG AAA CTG GTG GAC AAC AAC ACA      1303
Gln Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn Thr

GCA TTG GTT GAC AAA TTG AAG CGT TTC CAG CAG GAG AAT GAA GAA TTG      1351
Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu Leu

AAA GCT CGG ATG GAC AAG CAC ATG GCA ATC TCA AGG CAG CTT TCC ACG      1399
Lys Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser Thr

GAG CAG GCT GTT CTG CAA GAG TCG CTG GAG AAG GAG TCG AAA GTC AAC      1447
Glu Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val Asn

AAG CGA CTC TCT ATG GAA AAC GAG GAG CTT CTG TGG AAA CTG CAC AAT      1495
Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His Asn

GGG GAC CTG TGT AGC CCC AAG AGA TCC CCC ACA TCC TCC GCC ATC CCT      1543
Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile Pro

TTG CAG TCA CCA AGG AAT TCG GGC TCC TTC CCT AGC CCC AGC ATT TCA      1591
Leu Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile Ser

CCC AGA TGA CACGTCCCCA AAGTCCACAG ACTCTCTGAA AGCATTTTGA             1640
Pro Arg  *

TGCAGGTCTG CAGGACTGAC CCCAAGGAGG AACGTGGGCA CAAGAGGTAT ATCAGCACAC   1700

GTGTGATCAC CGTAGGTAAC TGGAGCGTCA CCACCGGCGG AATCGAGCTT CTGAGACTGG   1760
```

AAGTCTGGAG GAAGACTTTT GCCTCCGTCC AAAAGATTCC TCCAAAAAAA GATTTAAAAA 1820

AAGATTTCGG CATCGACACG GACGTTGTTG CACAAAGCAC TTAAAGAACG AGAGCATCTT 1880

GTTCATTGCC TTTTTCACCT AAGCATAAGG GGAAAAACTC TCAGGGCCCT ATTAAGATTT 1940

ATAACCTTTG TAATGTTCTT CACCACAGAC ACCTTCTTGT GAGTTTTCAG TCTGACTGTG 2000

GGGGTGGGGG GTGTGAATGA AATGGATGTC ACAGAGTGTC ATGTGTCTGA TGCAGCCTCC 2060

TCTGCTGTGT ATTAAATGTC AAAATCTGAA TATATCTGGA TATGTACTAA TCAAATAATA 2120

ATCAATCAAT CAGCATATAC ATTTCAGCCA AAGCCATAGA AGAAAAAGCA ATAGTTGCTT 2180

GAATTATGAT CATCTACCAC CAACTCTGCT CAGCCCTGTA ACAGGGTAGG GAGAGGGTAT 2240

AACAGGAAGA GCTTTGACTT GTCCCTGTCT ATACATTCTC TGTATCTTTT GGGGGTAACT 2300

TCTTGGCAGT TTTTCAGTGT TCAGCCATGT CAGTTGAAAC TAGATTTTTC TGTAGATTTT 2360

TTACTTACCC ATGTGAGCCT AACACTATCC TGTAATTCAT TTTCTCAGGC TATGTGTAAA 2420

TGTAGAACCC TAATTTTTCT ATAAAAAAAC AAACTAACTA ACTGTGTAAA GAAAGAAAAA 2480

GGGAAGTACC AATGGGTTTT TCCACCTTAT TTTTACCTTT GATCTACCCT TGCAGATTTA 2540

ACCTGTCTTC TTCCCTCCCA TTATTCTCAT TTTCCTTTTA CCTTTCTCCA CCATCCAGAG 2600

CCACAAAAGC AAACCTTCTA CCTCCTACCT ACTTTTCTCT GGGACAAGGA TAAAGGAATA 2660

TGATTTTCCA GAGCCCCAGA GCCAGCTCAT CTTCCAGGTG CTGAAACCAC TTTCCAAATA 2720

AACTAAAGCC TGGATTTGAT ATTACAAATT TTGGGAAATC TTAGAATAAA GAACGAGAAC 2780

AAGGAAGTCA TTGGCTAGTA TAATTAAGAA AGGTAGGATT CAGTGCTTAC CGATGATGCA 2840

GTACTTGATA GAAGAAAACA GTCTGGGAGG ATAGCGCTCA TTTTTCAGTT ACCCTTTAAG 2900

GAGTCCCTTT GTCTTTGGGA AAGTAGCAGA ATGGTCCGCT TCTTTCCCAT GAGTGGAAAA 2960

TGTGGCTTGT CCAACTCTCC TCCAGGTTGC ATTTCAGTTT CTTTCCAAAA CTTATTACCT 3020

CCCCTAATCC TGAGACTTTG GAAAAGGTGG AAGGAAGAAC TGTTGCTTTA TCTCCCCCTC 3080

CCTGCATGTG TCAACATTGT GATGTCAGTA TTTACTAATC TACATTCAGT GGCTGTACAA 3140

ATAACAGCTG TAGTAAGAAG AGATTCAGGA TGCTAGAGGT GAATATTTGG GTCATTTACA 3200

TGTACACTAC ATAGCAAGTT GATACTCATG TTGCATGTTC TTTTAAATTA GTGATTTTGT 3260

GTCTTAAGTC TTTAACTTCC AATACTTCAT CATGTATGTA ACCTTCCATG TTTGCTTCTG 3320

ATAAATGGAA ATGTAGGTTC ACTGCCACTT CATGAGATAT CTCTGCTCAC GCTTCCAAGT 3380

TGTTCTCAAT GACATTAGCC AAAGTTGGGT TTGCCATTCA TCCCCTAGGC ATGGTAAATC 3440

TTGTGTTGTT CCCTGCTGTC CTCCGTATTA CGTGACCGGC AAATAAATCT CATAGCAGTT 3500

AATATAAAAC ATCTTTGGAG GATGGGAGAG AACAGGAGGG AAGATGGGAA ACAAAATAGA 3560

GAATTCTTAA GATTTTGTTT AAACCAAATG TTTCATGTAG AATGCAAAAT GTTGGCACGT 3620

CAAAAATATG AATGTGTAGA CAACTGTAGT TGTGCTCAGT TTGTAGTGAT GGGAAGTGTA 3680

TTTTACTCTG ATCAAATAAA TAATGCTGGA ATACTCAAAA AAAAAAAAAA AAAAAAAAAA 3740

AA 3742

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 435 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Met Leu Leu Ser Pro Lys Phe Ser Leu Ser Thr Ile His Ile Arg Leu
1 5 10 15

Thr Ala Lys Gly Leu Leu Arg Asn Leu Arg Leu Pro Ser Gly Phe Arg
20 25 30

Arg Ser Thr Val Val Phe His Thr Val Glu Lys Ser Arg Gln Lys Asn
35 40 45

Pro Arg Ser Leu Cys Ile Gln Pro Gln Thr Ala Pro Asp Ala Leu Pro
50 55 60

Pro Glu Lys Thr Leu Glu Leu Thr Gln Tyr Lys Thr Lys Cys Glu Asn
65 70 75 80

Gln Ser Gly Phe Ile Leu Gln Leu Lys Gln Leu Leu Ala Cys Gly Asn
85 90 95

Thr Lys Phe Glu Ala Leu Thr Val Val Ile Gln His Leu Leu Ser Glu
100 105 110

Arg Glu Glu Ala Leu Lys Gln His Lys Thr Leu Ser Gln Glu Leu Val
115 120 125

Asn Leu Arg Gly Glu Leu Val Thr Ala Ser Thr Thr Cys Glu Lys Leu
130 135 140

Glu Lys Ala Arg Asn Glu Leu Gln Thr Val Tyr Glu Ala Phe Val Gln
145 150 155 160

Gln His Gln Ala Glu Lys Thr Glu Arg Glu Asn Arg Leu Lys Glu Phe
165 170 175

Tyr Thr Arg Glu Tyr Glu Lys Leu Arg Asp Thr Tyr Ile Glu Glu Ala
180 185 190

```
Glu Lys Tyr Lys Met Gln Leu Gln Glu Gln Phe Asp Asn Leu Asn Ala
        195                 200                 205

His Glu Thr Ser Lys Leu Glu Ile Glu Ala Ser His Ser Glu Lys Leu
    210                 215                 220

Glu Leu Leu Lys Lys Ala Tyr Glu Ala Ser Leu Ser Glu Ile Lys Lys
225                 230                 235                 240

Gly His Glu Ile Glu Lys Lys Ser Leu Glu Asp Leu Leu Ser Glu Lys
                245                 250                 255

Gln Glu Ser Leu Glu Lys Gln Ile Asn Asp Leu Lys Ser Glu Asn Asp
            260                 265                 270

Ala Leu Asn Glu Lys Leu Lys Ser Glu Glu Gln Lys Arg Arg Ala Arg
        275                 280                 285

Glu Lys Ala Asn Leu Lys Asn Pro Gln Ile Met Tyr Leu Glu Gln Glu
    290                 295                 300

Leu Glu Ser Leu Lys Ala Val Leu Glu Ile Lys Asn Glu Lys Leu His
305                 310                 315                 320

Gln Gln Asp Ile Lys Leu Met Lys Met Glu Lys Leu Val Asp Asn Asn
                325                 330                 335

Thr Ala Leu Val Asp Lys Leu Lys Arg Phe Gln Gln Glu Asn Glu Glu
            340                 345                 350

Leu Lys Ala Arg Met Asp Lys His Met Ala Ile Ser Arg Gln Leu Ser
        355                 360                 365


Thr Glu Gln Ala Val Leu Gln Glu Ser Leu Glu Lys Glu Ser Lys Val
    370                 375                 380

Asn Lys Arg Leu Ser Met Glu Asn Glu Glu Leu Leu Trp Lys Leu His
385                 390                 395                 400

Asn Gly Asp Leu Cys Ser Pro Lys Arg Ser Pro Thr Ser Ser Ala Ile
                405                 410                 415

Pro Leu Gln Ser Pro Arg Asn Ser Gly Ser Phe Pro Ser Pro Ser Ile
            420                 425                 430

Ser Pro Arg  *
        435
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1308 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

ATGTTGTTGT CTCCCAAATT CTCCTTATCC ACCATTCACA TACGACTGAC GGCCAAAGGA 60

TTGCTTCGAA ACCTTCGACT TCCTTCAGGG TTTAGGAGAA GCACTGTTGT TTTCCACACA 120

GTTGAAAAGA GCAGGCAAAA GAATCCTCGA AGCTTATGTA TCCAGCCACA GACAGCTCCC 180

GATGCGCTGC CCCCTGAGAA AACACTTGAA TTGACGCAAT ATAAAACAAA ATGTGAAAAC 240

CAAAGTGGAT TTATCCTGCA GCTCAAGCAG CTTCTTGCCT GTGGTAATAC CAAGTTTGAG 300

GCATTGACAG TTGTGATTCA GCACCTGCTG TCTGAGCGGG AGGAAGCACT GAAACAACAC 360

AAAACCCTAT CTCAAGAACT TGTTAACCTC CGGGGAGAGC TAGTCACTGC TTCAACCACC 420

TGTGAGAAAT TAGAAAAAGC CAGGAATGAG TTACAAACAG TGTATGAAGC ATTCGTCCAG 480

CAGCACCAGG CTGAAAAAAC AGAACGAGAG AATCGGCTTA AAGAGTTTTA CACCAGGGAG 540

TATGAAAAGC TTCGGGACAC TTACATTGAA GAAGCAGAGA AGTACAAAAT GCAATTGCAA 600

GAGCAGTTTG ACAACTTAAA TGCGCATGAA ACCTCTAAGT TGGAAATTGA AGCTAGCCAC 660

TCAGAGAAAC TTGAATTGCT AAAGAAGGCC TATGAAGCCT CCCTTTCAGA AATTAAGAAA 720

GGCCATGAAA TAGAAAAGAA ATCGCTTGAA GATTTACTTT CTGAGAAGCA GGAATCGCTA 780

GAGAAGCAAA TCAATGATCT GAAGAGTGAA AATGATGCTT TAAATGAAAA ATTGAAATCA 840

GAAGAACAAA AAAGAAGAGC AAGAGAAAAA GCAAATTTGA AAAATCCTCA GATCATGTAT 900

CTAGAACAGG AGTTAGAAAG CCTGAAAGCT GTGTTAGAGA TCAAGAATGA GAAACTGCAT 960

CAACAGGACA TCAAGTTAAT GAAAATGGAG AAACTGGTGG ACAACAACAC AGCATTGGTT 1020

GACAAATTGA AGCGTTTCCA GCAGGAGAAT GAAGAATTGA AAGCTCGGAT GGACAAGCAC 1080

ATGGCAATCT CAAGGCAGCT TTCCACGGAG CAGGCTGTTC TGCAAGAGTC GCTGGAGAAG 1140

GAGTCGAAAG TCAACAAGCG ACTCTCTATG GAAAACGAGG AGCTTCTGTG GAAACTGCAC 1200

AATGGGGACC TGTGTAGCCC CAAGAGATCC CCCACATCCT CCGCCATCCC TTTGCAGTCA 1260

CCAAGGAATT CGGGCTCCTT CCCTAGCCCC AGCATTTCAC CCAGATGA 1308

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CAAGCGTTCT CTCGGAGGAC A 21

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CGCGGATCCC AGACAGACCG GACGGAACTG GAG 33

(2) INFORMATION FORSEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CCGGAATTCA CTACAACCTT TCGTTTAAAG CATC 34